Brain

A Journal of Neurology

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BRAIN

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THE SURGICAL TREATMENT OF COLLOID CYST OF THE THIRD VENTRICLE

A Report Based Upon Twenty-one Personal Cases

BY

WYLIE McKISSOCK

(From the National Hospital, Queen Square, and St. George's Hospital)

The attention of neurological surgeons was brought sharply to bear upon the colloid cysts when Dandy in 1933 published his monograph on Benign Tumours of the Third Ventricle. He reported 31 cases where this condition had been found at necropsy and added 5 cases of his own in which surgical excision had been achieved with but a single post-operative death.

Since that time many papers have been written upon the subject, most reporting one or two cases with a good proportion of satisfactory surgical results. Grossiord (1941) collected some 76 cases from the literature and wrote an extensive monograph covering most aspects of the condition. Of this series 27 had been operated upon with 4 deaths. Greenwood (1948) in reporting 8 cases personally operated upon with one death, refers to some 60 cases in the literature with 15 successful operations for removal. No doubt there is some considerable overlap in these two series, but it is evident that many more of these tumours are coming to light with the increasing accuracy of clinical and radiological investigation. As the published figures reveal a considerable mortality following surgical removal of the tumour it has seemed reasonable to review the method of treatment; a death-rate of some 20 per cent is high for a purely benign lesion and every effort should be made to reduce it.

The reasons for failure in treatment may de divided into two groups; firstly, the anatomical situation and relations of the tumours, and, secondly, failure in accurate diagnosis.

Anatomy.—The colloid cyst is attached to the choroid plexus of the roof of the third ventricle to a very variable extent, sometimes by a narrow pedicle, at others by a broad sessile base. It is frequently attached to the

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choroid plexus passing through the foramen of Munro and may also be adherent to the terminal vein after its course along the gutter-like floor of the anterior horn of the lateral ventricle as it passes through the foramen to drain into the veins of Galen. Each of these anatomical considerations is of great practical importance in attempting surgical excision of a colloid cyst.

A wide basal attachment to the roof of the third ventricle will make excision difficult and, by causing undue traction on the cyst, may lead to hæmorrhage from the choroid plexus and damage to the lesser veins of Galen. Adhesion to the choroid plexus at the foramen may lead to arterial bleeding which, although controllable, may, in turn, lead to much more extensive manipulation of the ventricular walls with subsequent bruising or damage, and disturbance of function of the hypothalamic centres in the post-operative period. Such disturbance may be severe enough to lead to death from hyperthermia with or without hyperpnœa (fig. 1).

The terminal vein varying greatly in size, plays a comparably variable part in the venous return from the caudate nucleus. When large, and important in this function, its occlusion leads to fatal results with infarction of the basal ganglia. These three points are peculiar to the operation for removal of a colloid cyst and those to which special attention must be paid if a successful surgical result is to be achieved.

Diagnosis.—In many of the cases reported where death has followed operation it is evident that an accurate diagnosis has not been arrived at before operation and the first case in this series is an example of this failure to diagnosis.

H. A. W., a male aged 50, was referred by Dr. F. L. Golla in 1939, complaining that for six months he had suffered momentary attacks of severe pain beginning in the right face, spreading to the neck, arm and leg, followed by slight numbness in the affected parts with subsequent inability to walk for about fifteen minutes. The attacks occurred at intervals of a week or so, were sudden in onset and developed without warning. For one month he had been seeing double and during the week before admission to hospital there had been an episode in which he had suddenly burst into a flood of tears without any apparent cause.

Neurological examination.—Complete examination of the central nervous system disclosed only bilateral papillœdema with hæmorrhages.

Skull plates showed no abnormality.

Pre-operative diagnosis.—Unlocalized intracranial tumour.

Ventriculography.—Both ventricles were tapped and a large amount of fluid was obtained under increased pressure. The X-ray plates were unfortunately misinterpreted, the dilated lateral ventricles and imperfectly filled third ventricle being taken to indicate a lesion in the posterior fossa. Subsequent review of the films by Bull and Sutton revealed a filling defect in the region of the foramina of Monro characteristic of a colloid cyst.

Operation.—A suboccipital exploration and decompression was performed which revealed no abnormality other than greatly increased pressure and precipitated the death of the patient on the third post-operative day.

Post-mortem.—A typical colloid cyst, measuring about 1·5 cm. in diameter, was exposed.

Here was a case where clinical examination could not have given the correct localization and where inexperience in the interpretation of the ventriculogram led to an incorrect localization of the cause of the hydrocephalus, a wrongly planned surgical approach and a fatal outcome.

Very occasionally, even ventriculography may fail to disclose the position and pathological nature of the tumour, and this also may lead to an incorrect surgical procedure.

A. E., a man aged 42, was admitted to hospital in February 1948 complaining of short-lived headaches for the last eighteen months. The headaches were occipital, severe, continued for two to five minutes and disappeared as suddenly as they came. He thought that sitting or lying down relieved the pain, even during the last three months, when they had been much more frequent and severe. Blurring of vision had been noted in association with some of the headaches.

Neurological examination.—The only abnormal physical findings were chronic bilateral papillœdema and a left-sided central scotoma.

Skull plates.—No abnormality was found.

Pre-operative diagnosis.—Unlocalized intracranial tumour.

Ventriculography.—The lateral ventricles were dilated, there was a block in the region of the foramina of Monro but no filling defect in the third ventricle could be demonstrated as neither air nor myodil could be made to enter this cavity.

Operation (11.2.48).—A bilateral Torkildsen's short circuit was performed.

Post-operative course.—Recovery was slow but the patient was well enough to leave hospital four weeks after operation only to return two weeks later with an exacerbation of headache and increasing papillœdema.

Operation (1.4.48).—Through a right-sided concealed hypophyseal incision the right lateral ventricle was entered by means of a 3 cm. incision in the frontal lobe. A colloid cyst was totally removed without difficulty and without damaging the terminal vein.

Post-operative course.—Although the patient recovered well initially, he soon became drowsy, the temperature, pulse and respiration rates steadily increased and he passed into a coma in which he died on the seventh day.

No post-mortem was obtained.

It was evident that this patient had an obstructive lesion in the third ventricle and it was wrongly assumed that this was an inoperable one. This error led to a palliative operation in place of a radical one. Unfortunately a post-mortem was refused by the relatives and the cause of death was not proved. Clinically the cause of death was disturbance of the hypothalamic centres.

The frequency with which colloid cysts produce sudden unconsciousness followed by death, emphasized by Kelly, may make correct diagnosis and appropriate surgical treatment difficult. Temporizing in such cases may well be fatal. The well-established neurosurgical procedure of ventricular drainage, so valuable in decompressing patients with cerebellar tumours and temporarily avoiding a possible disturbance

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from ventriculography, is here absolutely contra-indicated. Improvements may result but so also may a fatal issue.

M. H., a woman aged 48, was admitted to hospital in deep coma. The accompanying notes told of a ten-day history only, beginning with severe constant vertical headaches. Four days previously she became drowsy and sudden unconsciousness took place three days before admission.

Clinical examination revealed irregular, fixed, and unequally dilated pupils, a spastic hemiparesis with bilateral extensor plantar responses.

Radiograms of the skull showed only slight osteoporosis of the dorsum sellæ.

An immediate ventriculogram showed symmetrically dilated lateral ventricles and no filling of the third ventricle. A diagnosis of a third ventricle tumour was made and ventricular tapping resorted to in an effort to improve the physical state of the patient. No amelioration took place and the patient died the following day.

At post-mortem a typical small colloid cyst completely blocking the foramina of Monro was revealed (fig. 2).

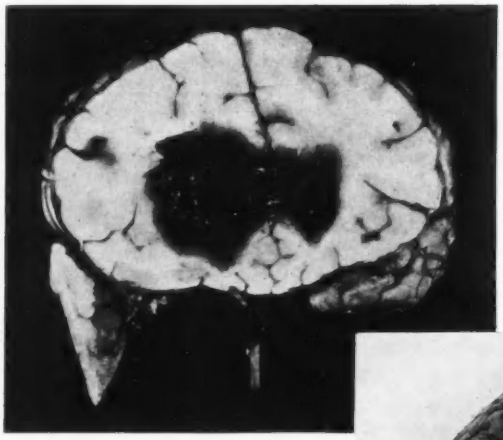

FIG. 1.—Photograph of coronal section of brain showing extensive hæmorrhage into the basal ganglia and ventricular system due to occlusion of the terminal vein.

FIG. 2.—Photograph of brain after division of the corpus callosum to show typical colloid cyst in patient M. H.

Whether a diagnosic ventriculogram followed by excision of the tumour could have saved this patient must remain a matter of speculation, but it is certain that ventricular drainage, even bilateral, was of no avail.

It is evident, therefore, from what has been said that rapid accurate diagnosis is essential, incorrect surgical procedures lead only to disaster, and certain hazards attending total excision have to be overcome if treatment is to be successful.

Surgical Approach

Dandy advocated a posterior parietal approach splitting the corpus callosum and attacking the tumour from behind and above if it appeared to be well back in the third ventricle. When more anteriorly placed he advised an anterior approach of the concealed hypophyseal type.

Greenwood considers this posterior approach more difficult, advises a frontal flap with splitting of the anterior part of the corpus callosum, reaching the lesion from above and in front. He disapproves of the transcortical approach through the lateral ventricle in view of the risks of traumatic epilepsy developing later.

Dandy unfortunately gives no details of the neurological state of his patients post-operatively so that the presence or not of a hemianopia is unknown: However, this is not an uncommon sequel of surgical attack upon the pineal region and might be expected in, at any rate, a proportion of cases operated upon by the posterior parietal method.

Splitting the anterior part of the corpus callosum involves a risk of damaging the anterior cerebral artery with its many branches running laterally to the frontal pole.

In describing the transcortical method most authors advise, or show by drawing and photograph, the turning of quite a large scalp and bone flap followed by excision of a core of frontal lobe extending down into the lateral ventricle. In one of Dandy's cases for example the weight of the excised portion of frontal lobe is given as 49·7 grammes. It is difficult to believe that, in the light of the sequels of leucotomy and lobectomy, some defect in the intellectual or emotional spheres does not follow such extensive excision of frontal cortex. It is true that damaging the frontal cortex may produce a subsequent traumatic epilepsy but it is believed that this risk is not unduly great and that the simplicity of operation by this route justifies the slightly increased risk of this complication ensuing.

Large exposures are unnecessary when dealing with the colloid cyst, for the tapping of dilated lateral ventricles provides a means of controlling any tendency to herniation of the brain through a small dural opening. The eventual field of operation is only 1·5 to 2 cm. square and

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it is unnecessary to expose more cerebral cortex than is required to gain access to the ventricle.

Surgical approach.—It is suggested that a scalp flap of the concealed hypophyseal type, but lying rather further back, provides adequate space for the turning of a bone flap measuring about 6 cm. square (fig. 3). A dural flap 4 cm. square is then cut and turned medially.

FIG. 3.—X-ray of skull showing small size of flap used for the suggested approach. This post-operative ventriculogram also shows reconstitution of normal ventricular system, there being no evidence of colloid cyst remaining in the region of the foramina of Monro.

Tapping of the dilated lateral ventricle reduces the intracranial tension and enables a 3 cm. incision to be made through the frontal cerebral cortex and extended deeply until the lateral ventricle is entered. Flat brain retractors will hold the edges of this incision quite wide enough apart to provide an excellent view of the interior of the ventricle and will enable the foramen of Monro to be identified. In most cases the foramen is found to be enlarged with the wall of the colloid cyst bulging into it, possibly adherent to the choroid plexus and terminal vein.

The next stage of the operation consists in tapping the cyst, without enlarging the foramen by dividing its anterior margin and extracting the contents either by suction or by squeezing the cyst with untoothed dissecting forceps passed through the foramen.

When collapsed, the cyst is drawn through the foramen and dissected free from the terminal vein and choroid plexus. It is finally held up in the empty lateral ventricle and coagulated. A tiny mass of coagulated

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tissue alone remains which, when released from the forceps, disappears through the foramen into the roof of the third ventricle. Thus is the obstruction to the flow of the cerebrospinal fluid relieved.

The small incision in the cortex may be covered with fibrin foam or film, or by gelatin film, to prevent its adhesion to the overlying dura which is next sutured with fine black oiled silk. After replacing the bone flap, periosteum, galea and skin are closed with interrupted silk sutures.

Material and Results

In the last eleven years 21 patients with colloid cyst have been encountered of whom 15 are living at the present time. These 21 cases have been reviewed clinically by Kelly, and most of them were included in the report on ventriculographic diagnosis by Bull and Sutton.

From 1939 until 1946 inclusive, total excision was the aim and the 6 cases of the period were all subjected to operation. In 5 of the 6 cases total excision was achieved, 3 of the patients surviving, the 2 deaths being due to damage to the basal ganglia as a result of occluding the terminal vein. The sixth patient in this series was incorrectly diagnosed, a suboccipital decompression was made and the patient succumbed the following day (H. A. W. reported above).

In the last three and a half years from January 1947 to the time of writing, 15 patients with colloid cysts have been met with and operated upon. In 2 of these cases death followed and in each case the diagnosis of colloid cyst was not made pre-operatively, one being treated by Torkildsen's short circuit and subsequent excision of the cyst two months later (A. E. reported above), whilst the other, admitted in coma of three days' duration (M. H. reported above), succumbed after ventriculography and repeated ventricular taps.

The remaining 13 patients were all diagnosed pre-operatively as cases of colloid cyst and were treated according to the outline given above, 2 of the patients being operated upon by Mr. Valentine Logue. In 3 of the 13 the neck of the cyst was easily visible and could be divided between tantalum clips so that the tumour was completely removed whilst the other 10 were treated by coagulation of the capsule. All 13 cases recovered but one suffered a recurrence fifteen months later and it is known that he died following another operation. There is no evidence of recurrence of symptoms or physical signs in the 12 other patients.

The single case of recurrence does not, it is felt, invalidate the method of treatment advised. A second operation if recurrence takes place, should, of course, be designed to remove the tumour completely and will thus carry a mortality rate of the order of 20 per cent or more but

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the operation should not be one of any greater difficulty than if undertaken initially. On the other hand the operative treatment advocated, when the diagnosis has been established, has not been attended by a single death. This is in sharp distinction to all other reported series of cases.

RESULTS OF TREATMENT OF 21 PATIENTS WITH COLLOID CYST

Totals

Correct Pre-operative Diagnosis	*Incorrect Pre-operative Diagnosis*
18 cases. 3 deaths. 16·6 per cent mortality	3 cases. 3 deaths. 100 per cent mortality

Before Revised Treatment 1939–46

Correct Pre-operative Diagnosis	*Incorrect Pre-operative Diagnosis*
5 cases. 2 deaths. 40 per cent mortality	1 case. 1 death. 100 per cent mortality

After Revised Treatment 1946–50

Correct Pre-operative Diagnosis	*Incorrect Pre-operative Diagnosis*
13 cases. 0 deaths. 0 mortality	2 cases. 2 deaths. 100 per cent mortality

Of the 15 patients who survived operation.

11 are symptom free, working and show no abnormality in the central nervous system.

1 is working, has no abnormal symptoms or signs but has suffered a single convulsive attack.

1 is working but hampered by blindness of the right eye from consecutive optic atrophy.

1 is not working. This patient was a known epileptic before operation. Whilst physically well he is now mentally deteriorated and continues to have occasional generalized epileptic attacks.

1 died fifteen months later after operation for recurrence of the tumour.

SUMMARY AND CONCLUSIONS

(1) A series of 21 personal cases of colloid cyst is reported with recovery in 16 cases.

(2) The anatomical and diagnostic difficulties are discussed and emphasis laid upon the need for exact pre-operative diagnosis.

(3) Previous methods of surgical approach and treatment are discussed and criticized.

(4) A modified form of surgical approach with electro-coagulation of the cyst advocated which, *when the pre-operative diagnosis was correct,* led to recovery in the last 13 consecutive cases.

(5) It is stressed that an incorrect diagnosis leads almost certainly to death.

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THE EFFECTS OF B.A.L. IN HEPATOLENTICULAR DEGENERATION

BY

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It was shown in an earlier paper (Cumings, 1948) that the liver and some areas of the brain, more particularly the basal ganglia, contain an excess of copper in hepatolenticular degeneration. It was suggested in that paper that the therapeutic effect of 2,3-dimercaptopropanol (B.A.L.) was worthy of trial, as Mandelbrote *et al.* (1948) had shown that it could produce an increased urinary excretion of copper. This paper records the results of such a trial in 4 patients with this disorder.

Materials and Methods

7 patients have been examined, of whom 4 adults were considered clinically to be suffering from hepatolenticular degeneration, while the remainder, acting as controls, consisted of one child suffering from epilepsy associated with hepatomegaly and with evidence of liver damage, and another child and an adult both of whom showed tremor and involuntary movements but without a Kayser-Fleischer ring, and with no clinical evidence of hepatolenticular degeneration.

The biochemical studies consisted of blood copper estimations, and of 24-hourly urinary excretion levels of copper and amino-acid nitrogen before, during and after B.A.L. Liver function tests were performed initially and at varying stages of the period of study. Copper was estimated essentially by the method of Eden and Green (1940) but using for serum a trichloracetic acid filtrate as Mann and Keilen (1938) have shown that this method of deproteinization liberates any bound copper, and recovery is complete. For urine 25 ml. or 50 ml. of each well mixed 24-hourly sample was taken, heated till dry and then dry ashed at 560° C. in a muffle furnace, after which the usual technique was followed. A photo-electric colorimeter with a filter of 460 $m\mu$ was used for the measurement of the colour. Special care had to be taken to see that all receptacles for the urine and all syringes for the collection of blood were copper free, as well as all the apparatus used; control blanks were put up each time. Amino-acid nitrogen in the urine was estimated by the formol titration technique (Hawk, Oser and Summerson, 1947).

The following liver function tests were performed on serum—total protein, albumen, Takata Ara, thymol turbidity, colloidal gold, alkaline phosphatase, amino-acid nitrogen and the van den Bergh reaction. A pyruvate tolerance test (Joiner, Thompson and Watson, 1950) was performed on a few of the cases, using the method of Friedemann and Haugen (1943) for the estimation of pyruvate in the blood.

After initial control periods for preliminary clinical and biochemical examinations B.A.L. was administered to the adults in the following dosage, which Professor R. H. S. Thompson had suggested to me:

Day 1. 4 ml. of a 5% solution 4 times during the day subcutaneously.
" 2. 4 " " " " " twice " " " "
" 3. 4 " " " " " " " " " "
" 4. 4 " " " " " once " " " "
" 5. 4 " " " " " " " " " "
" 6. 4 " " " " " " " " " "

The dosage for the children was half of the above.

The blood and urinary levels of copper and amino-acid nitrogen were followed for a few days after cessation of treatment. After an interval of about two weeks a further course was given, and up to four courses were administered in one patient.

Results

Clinical.—To the pathologist undoubted improvement followed the administration of B.A.L. in two of the patients with hepatolenticular degeneration, and this improvement was maintained during their stay in hospital. No improvement was seen in one patient with this disease, nor in the three control cases. The other patient with hepatolenticular degeneration said she felt a little improvement but no real alteration could be found that might not have been due to the normal variations to be found in this disease. There are included at the end of this paper brief descriptions of each of the four patients suffering from hepatolenticular degeneration by the physicians under whose care they were while in hospital, together with their views as to the effects of the therapy given.

Biochemical.—2 of the 4 cases of hepatolenticular degeneration showed liver dysfunction, the other 2 none. At present only the 2 former patients will be considered.

(*a*) *Liver function:* The biochemical changes found can be seen in Table I, which shows the results of the examinations on admission and those prior to discharge. The first patient had 11 such examinations and Case 2 three series of tests between courses of B.A.L., and these demonstrated slow but definite improvement. It is worth noting that in Case 2 the serum amino-acid nitrogen on admission was above normal, but fell following treatment, whereas in the other case the serum levels did not change, nor were they much above the normal.

Table I

Test	Case 1: No. 16399/49.		Case 2: No. 23815/50.	
	Before B.A.L.	After B.A.L.	Before B.A.L.	After B.A.L.
Total protein (grammes/100 ml.)	6·1	6·27	6·78	6·48
Albumen (grammes/100 ml.)	2·7	2·6	3·55	3·42
Alkaline phosphatase (units)	10·0	14·0	17·6	8·0
Thymol turbidity (units)	4·5	4·0	8·0	4·0
Colloidal gold	Positive (2)	Positive (1)	Positive (1)	Positive (1)
Van den Bergh (mg./100 ml.)	2·0	1·0	2·0	0·75
Amino-acid nitrogen (mg./100 ml.)	8·0	9·0	12·0	5·56
Takata-Ara	+ + +	Weak positive	Weak positive	Very weak positive

Case 2 showed a diminished pyruvate tolerance, the results of this examination before and after treatment (3 courses) can be seen in Table II.

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TABLE II

Case 2 (No. 23815/50).	Pyruvate tolerance test. (Results expressed as mg. pyruvic acid/100 grammes blood).		
	0 min.	60 min.	90 min.
Before B.A.L.	1·18	0·93	1·39
After B.A.L.	0·66	1·07	1·40

(*b*) *Blood copper:* The blood levels before treatment in Cases 1 and 2 were 173 and 180 μg per 100 ml. and before discharge 203 and 116 μg per 100 ml. respectively. However, the effects of B.A.L. on the blood copper can best be seen in fig. 1 which shows the variations throughout the first three of the courses of treatment given him.

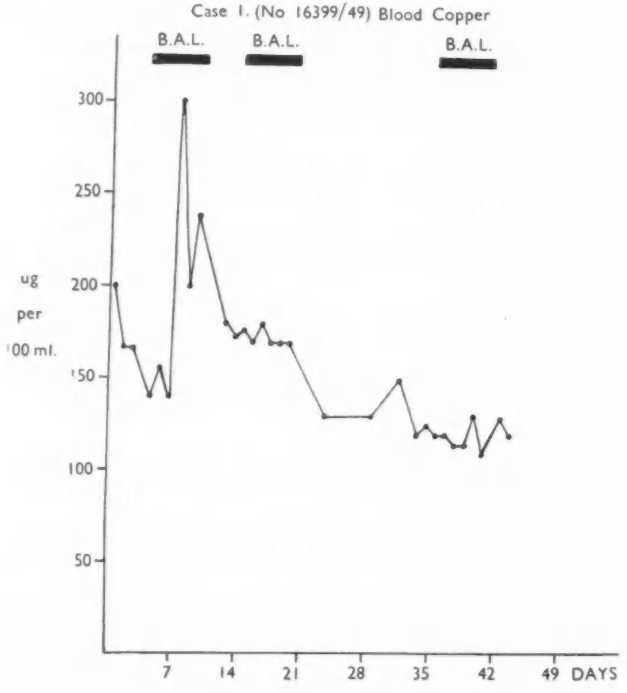

FIG. 1.

Normal figures for blood copper can be considered to be up to about 120 μg–150 μg per 100 ml. according to Thompson and Watson (1949) and Mandelbrote *et al.* (1948).

It can be seen that there was a marked increase in the blood level which commenced a few days after starting the injections. Succeeding courses did not produce such well-marked changes, in fact no appreciable

alteration took place during the third course of treatment, and the blood levels were not followed during the fourth course. As a result of this finding, and in view of the difficulty experienced in obtaining such a large series of specimens in all such cases, owing to the violence of the tremor, blood levels were not so extensively followed in all the other patients, more especially as the daily urinary output of copper, with an occasional blood level, was found adequate for the control of treatment.

(c) Urine copper and α amino-acid nitrogen: Normal figures for copper can be accepted as up to 10 μg per 100 ml. (Mandelbrote *et el.*) and 0·4 to 1·0 gramme per day (Hawk, Oser and Summerson) for amino-acid nitrogen using the techniques employed here.

The results in Cases 1 and 2 of the effect of B.A.L. on the urinary excretion of these two substances can be seen in figs. 2 and 3.

A number of interesting points emerge. Both patients before treatment showed an increased excretion of both copper and amino-acid nitrogen. Excretion of copper increased immediately B.A.L. was given, and prior to the rise in the blood copper, as can be seen when comparison is made between fig. 2 and fig. 1. This urinary copper increase was seen each time B.A.L. was given, but was much less marked after a number of courses. Amino-acid nitrogen levels fluctuated from day to

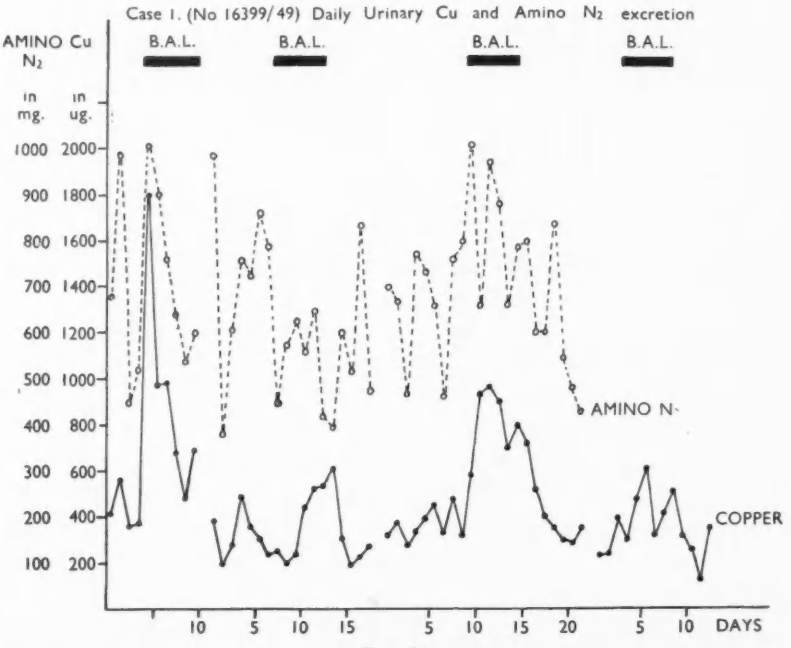

FIG. 2.

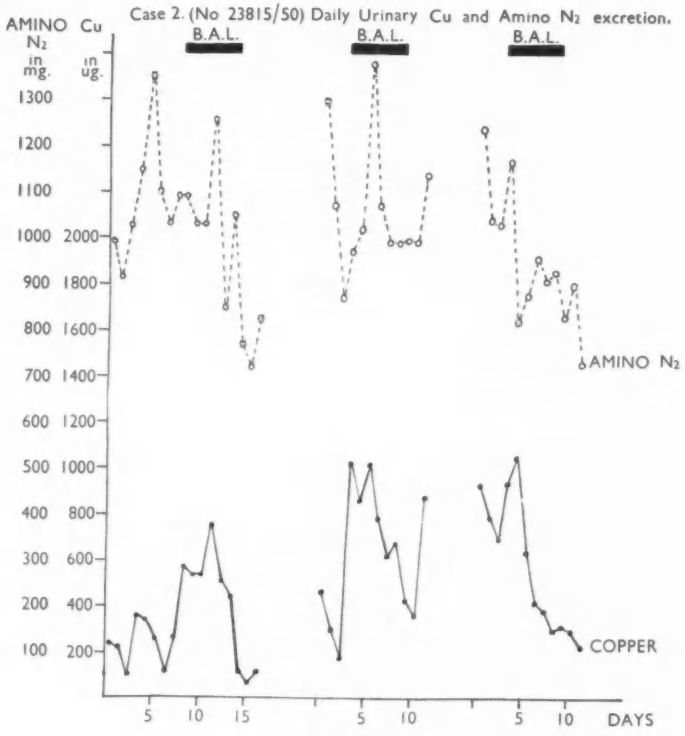

FIG. 3.

day, but were mainly raised throughout and were unaffected by therapy. Both these patients improved clinically during treatment.

The other 2 patients with hepatolenticular degeneration both had normal liver function tests, and one also showed a normal pyruvate tolerance test before and after B.A.L.; the pretreatment blood copper levels were normal, being 86 and 148 μg per 100 ml. Treatment caused no significant alteration in these levels.

The urinary excretion of copper and amino-acid nitrogen are to be seen in figs. 4 and 5.

It is seen that Case 3 had a somewhat raised copper but normal amino-acid nitrogen output, but that in the other patient these findings were reversed. The former patient had a serum amino-acid nitrogen of 6·9 mg. per 100 ml., but Case 4 with a raised urine amino-acid nitrogen showed a slightly raised blood level of 10·3 mg. per 100 ml. B.A.L. had no effect on either urinary copper or amino-acid excretion and neither patient improved clinically.

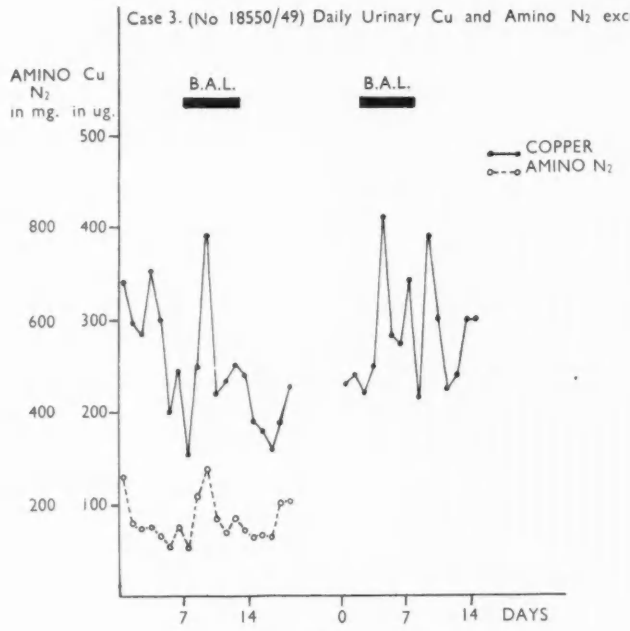

FIG. 4.

One of the 3 control patients had liver dysfunction as evidenced by biochemical tests, and he was a boy of 7 years. His blood copper was 148 μg per 100 ml., urinary copper was 68 μg a day, and amino-acid nitrogen excretion 0·227 gramme in twenty-four hours. The child, aged 9, who had involuntary movements, gave figures of 250 μg per 100 ml., 105 μg a day, and 0·389 gramme a day respectively, and in the adult with tremor figures of 111 μg per 100 ml., 64 μg a day, and 0·135 gramme a day respectively were obtained. This last patient's serum amino-acid nitrogen was 6·9 mg. per 100 ml.

Single courses of B.A.L. were given to these three control patients, but no significant alteration in the levels of either copper or amino-acid nitrogen in blood or urine took place. No clinical alterations were noted.

DISCUSSION

It has earlier been shown that there is retention of copper in the tissues in hepatolenticular degeneration (Haurowitz, 1930; Glazebrook, 1945, and Cumings, 1948) and that the urine may contain an excess of copper (Mandlebrote *et al.*, 1948, and Porter, 1949). Uzman and Denny-Brown (1947) and also Porter have shown that there may be an increase of α amino-acid nitrogen in the urine. 3 of the 4 patients reported in this

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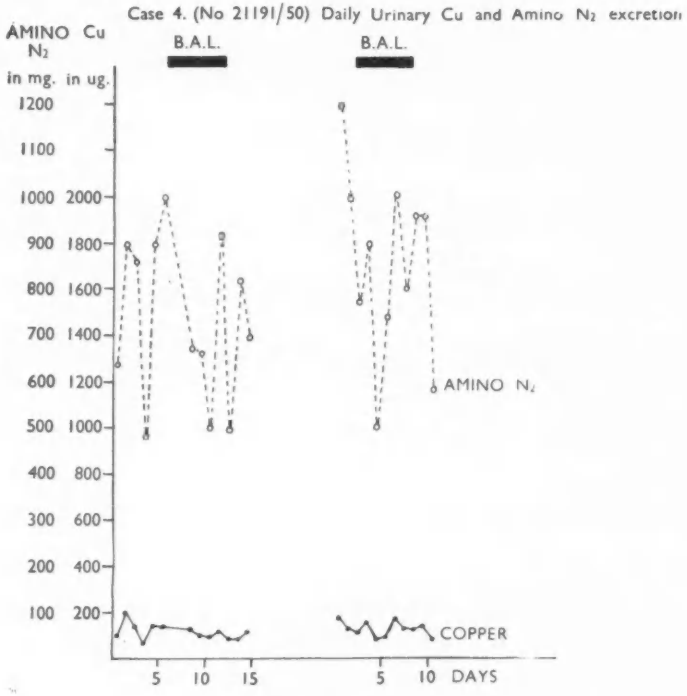

FIG. 5.

paper showed an increased copper and 3 an increased amino-acid excretion, but in both those showing liver dysfunction there was an increased excretion of both these substances. The amino-acid nitrogen levels in the blood were not appreciably raised although they were slightly increased in 2 of the patients. B.A.L. has been shown by Porter (1949) to produce an increased output of copper in the urine in hepatolenticular degeneration, but with no significant alteration in amino-acid nitrogen excretion. One of Porter's cases is said to have maintained improvement for up to five months, but the other showed no improvement. The findings recorded here show the same type of result. B.A.L. produced a considerable output of copper, more especially in the cases that improved clinically. There appear from the papers so far published to be two different biochemical abnormalities, namely, an increased copper and an increased amino-acid nitrogen excretion in the urine.

The findings in this investigation have confirmed that such abnormalities may be found either together or separately, but where there was liver dysfunction both these abnormalities were present.

Cooper *et al.* (1950) recently in an investigation in patients with hepatolenticular degeneration found a raised amino-acid nitrogen urinary excretion, and suggested that there was a lowered renal threshhold for amino acids, but they give no indication of the blood levels. The investigations recorded here showed that the blood serum amino-acid nitrogen levels were normal or only slightly above normal, and this finding, taken in conjunction with the increased amino-acid nitrogen excretion, would support Cooper's suggestion, even though it was not possible to estimate only the amino-acid nitrogen. It might have been expected that patients with advanced liver disease would show a raised blood amino-acid nitrogen level. However, administration of B.A.L. produced no alteration in the urinary excretion rate even though the liver functions, previously abnormal, improved. Further, the child with hepatomegaly showed no such urinary abnormality; so that it is unlikely that the liver condition influenced the amount of excretion of amino-acid nitrogen in these patients, and the suggestion of Cooper *et al.* seems to be the most probable explanation for this abnormality, but it is not yet possible to formulate a theory to explain these two abnormalities found in this disease.

Considering the diagnostic value of chemical investigations, it seems that an increased urinary copper and amino-acid nitrogen will be found in patients with liver damage. The blood copper levels may also be raised, at least to a figure higher than either Thompson or I have found in normal subjects, which would appear to be not higher than 150 μg per 100 ml. As far as I have seen up to date no other disease shows these features.

The experience that has been gained during the study of these cases, and perhaps more particularly the satisfactory results of therapy in Case 2, have indicated that it might be of advantage to administer short courses of B.A.L. at intervals, and this procedure is to be adopted in Case 2 in the hope that his present improved condition may be maintained. It is further recommended that such intermittent treatment shall be given for other cases that improve under the standard therapeutic measures suggested earlier. It is hoped that by this means the benefit derived from B.A.L. may be prolonged, but it is too early to be able to say how long such improvement will last.

Summary

Investigations into the content of copper and amino-acid nitrogen in blood and urine in 4 cases of hepatolenticular degeneration and in 3 control subjects are recorded before, during and after B.A.L. therapy.

It has been shown that before treatment there is an increase of one or both of these substances in the urine in all cases of hepatolenticular

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degeneration. Liver dysfunction was present in only 2 of these patients and it was in this group that improvement, both clinical and biochemical, took place during their stay in hospital. Urinary excretion of copper, but not amino-acid nitrogen, was lowered in the two patients that improved.

The control group showed no chemical abnormality in the urine, nor did B.A.L. influence the clinical conditions or alter the copper and amino-acid nitrogen excretion in the urine.

I wish to express my thanks to all the physicians under whose care these patients were, and more especially to those who have written the following abstracts of their cases and whose patients I was invited to treat.

I would also like to record the very considerable help given me in the technical work by Mr. H. Goodwin, to whom my thanks are due.

APPENDIX OF CASE RECORDS

By Dr. Denis Brinton.

Case 1 (No. 16399/49). A man of 36 who noticed three years before admission a shaking of the left hand which gradually increased in severity over three months. One to two months later the right hand became similarly affected, and he began to have difficulty in feeding himself. Following this he developed a side to side rotation of the head, while the tremor of the hands became worse, affecting also the arms. Shortly afterwards his legs also became affected.

A year before admission his speech became affected, because of lack of control over his breathing.

For two years he had generalized headaches. No history of jaundice or intestinal upset of any kind was obtained.

On admission to hospital there was slow slurring dysarthria, punctuated by long, deep stridulous inspiration. Bilateral Kayser-Fleischer rings, with arcus senilis on top, were present; no nystagmus was found.

Side to side flexion/extension tremor of the hands, varying in amplitude, getting worse on movement or on the least tension of the muscles was present; the direction of attention to his limbs resulted in mild tremor, which rapidly increased in violence, becoming worse distally, resembling a wing-beating appearance. The trunk then also became involved, shaking from side to side, with trunk rotation.

The legs were less severely and less frequently affected, the movement being one of abduction-adduction at the hips with a rotary element, of similar rate and nature as the upper limbs. There was no tremor at all during sleep. He was unable to get up from his bed.

Treatment.—He was given four courses of B.A.L. On each occasion there was considerable nausea, with vomiting on the first occasion; he was drowsy throughout each course and for three to four days afterwards. On each occasion there was marked improvement. After the first course he was able to stand unsupported and to walk a few steps, neither of which he could do before. The action tremor in the upper limbs was less marked.

After the second course of B.A.L. he rapidly improved, was able to walk about the ward, talk to other patients, and with difficulty place a cigarette in his mouth. He was still unable to feed himself.

By the time of his discharge eight months after admission, he was able to get out of the hospital himself and go for walks in the neighbourhood.

As far as can be ascertained this improvement was only maintained for about two or three months after leaving hospital.

By Dr. Denis Williams.

Case 2 (No. 23815/50. A man of 24 with healthy parents and six younger siblings all well, was admitted in May, 1950. No family history of nervous or mental disease. He complained that in 1946 he lost his job on account of nerves. In early 1948 his speech had become slowed and a few months later the right hand began to shake. In November, 1949, the left hand became slightly affected and two months later the left leg in addition. Three months prior to admission he had been unable to feed or shave himself on account of increased tremor. His general health was excellent. He considered that his memory was unchanged. There was no history of jaundice.

On examination he was cheerful and co-operative with a typical set expression and slowly fading smile, characteristic of his condition. Speech was slowed with mild slurring dysarthria. Both corneæ showed a typical Kayser-Fleischer ring, but otherwise the cranial nerves were normal. In the upper and lower extremities, nutrition, power and posture were normal, but tests of co-ordination were poorly performed and there was a pronounced intention tremor in the upper extremities, right more than left; any attempted movements produced an irregular fast tremor which increased in amplitude on persistence of effort. Similarly a less marked tremor was present in the left leg. Tone was slightly increased in both arms and left lower extremities. Sensation was normal throughout and all tendon reflexes were present and equal with bilateral flexor plantar responses. Abdominal reflexes were present and equal.

General examination and X-ray of the skull showed no abnormality.

After the first course of B.A.L. improvement occurred—notably the tremor was less marked; walking had improved; the facial expression

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was much less set; he was able to feed and shave himself for the first time for months. This improvement was maintained and the second course of B.A.L. was given in June. Thereafter there was no significant alteration in his state but the degree of improvement noted after the first course was maintained. A third course was given in July.

The patient was finally examined on September 28. He had been living a quiet town life in an hotel and had been travelling around London in public vehicles himself. He was eating alone in public places, shaving himself, and was responsible for all his personal affairs. On examination he walked rather stiffly, without any striking defect. His face lacked expression, but the foolish grin so characteristic of the condition was not now present. It is worth mentioning that his family abroad had commented on the improvement in his expression in photographs which they had received. His speech was rather flat and monotonous, and there was dysarthria for polysyllabic words. There was a marked coarse tremor of the hands at rest, the right being the more affected, but this ceased in voluntary movement. Co-ordination was less impaired than at the first interview and the limbs were less rigid.

Mentally he was probably unchanged although his father thought him improved. A reasonable summary of the clinical state is that there had been no deterioration in any way of his symptoms; that there had been slight but certain improvement in all his physical shortcomings after having had B.A.L. and that this improved state had remained for three months.

By Dr. J. St. C. Elkington.

Case 3 (No. 18550/49). A man, aged 27, was admitted to hospital with a five years' history of increasing tremor of his limbs and trunk and alteration of his speech. His family history was negative. His early childhood was healthy, but at the age of 18 he suffered from "yellow jaundice." He was severely ill for three months and believes that he was delirious and hallucinated and was thought to have meningitis. His recovery was ultimately complete and he remained healthy through adolescence.

His symptoms began at the age of 22 when he had already been serving for two years in the R.A.F. His symptoms began with tremor in the left arm which gradually increased in severity and spread first to the left leg and then to the right arm and finally to the right leg and trunk. This tremor became more violent as time went on and was always worse in carrying out purposive actions and when under observation. Two years after the onset of tremor be began to notice that his speech was becoming slow and jerky and he was troubled by increasing salivation.

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The patient has noticed no alteration of his mentality or emotional state and had experienced no difficulty in chewing or swallowing and was completely free from pain.

On examination at rest the patient was a tall sparsely-built youth lying in bed with an expressionless face, half-open mouth and retracted lips. His speech was slow and explosive, and words and syllables being interrupted by pauses. His mood was euphoric and his manner somewhat fatuous and childish but his intellect was normal for his occupation and education. Little tremor was to be seen at rest, but on attempting to carry out any purposive movements his limbs and trunk were thrown into a coarse tremor which increased in amplitude and violence throughout the attempted movement. The severity of the tremor made the estimation of muscular tone difficult, but it was probably normal and there was no loss of power in any muscle groups. Sensation was everywhere normal and both deep and superficial reflexes were natural.

General medical examination was negative and in particular no enlargement of the liver or spleen could be detected. There was a well marked Kayser-Fleischer ring of pigmentation around each cornea.

Progress.—This patient was observed in hospital for a number of weeks during which he received treatment with B.A.L. He reported improvement in his symptoms, but no decrease in his tremor could be observed, nor was there any improvement in the amount he could do for himself. It was thought that the subjective improvement was to be explained on the basis of his sanguine and suggestible temperament.

By Dr. J. St. C. Elkington.

Case 4 (No. 21191/50). A woman, aged 21, was admitted to hospital complaining of disturbance of speech and tremor of the arms of six years' duration. Her past history was healthy and there was no record of an attack of jaundice. Both parents, a sister aged 12 and a brother aged 5 were all well.

The patient was in good health until about the age of 16, when it was noticed that her speech was becoming indistinct. Shortly afterwards she developed a rhythmic tremor of the upper limbs especially on the left side which gradually progressed in severity until she could only feed herself with difficulty. Later the tremor extended to the muscles of her trunk and neck and her laugh became uncontrolled and more like a scream than normal laughter.

On examination she showed a mild degree of intellectual deterioration. The left pupil was larger than the right and either eye adducted on attempted accommodation. There was a well-marked ring of corneal pigmentation of both eyes typical of a Kayser-Fleischer ring. The upper

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lip was drawn upwards and movements of the lip were restricted when talking. There was a well-marked side-to-side tremor of the head and of the fingers and wrist on the left side. This was also present at the left shoulder when the arm was adducted. Occasionally similar movements were seen in the legs.

The left hand was held in a position of flexion at all the joints. On movement gross involuntary movements became apparent in both arms, more marked on the right side. Her gait was unsteady and she walked on a broad base.

There was no enlargement of the liver or spleen.

Treatment in hospital was associated with a subjective improvement in symptoms and it was thought by those in daily touch with the patient that there was some diminution in the severity of the tremor. This, however, was not sufficiently marked to be more than might be accounted for by suggestion and improvement in morale. Further observation in the out-patient department after discharge continues to record improvement. The patient states that she is now able to dress and feed herself. There is, however, no definite change in the physical signs.

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COLLOID CYSTS OF THE THIRD VENTRICLE

Analysis of Twenty-nine Cases

BY

REGINALD KELLY

(From the National Hospital, Queen Square)

Since Dandy (1933) published his monograph upon them there has been an increasing interest in these benign tumours; an interest that has been associated with technical advances in the operative approach and in a decline in the mortality of the operation. Unfortunately, in spite of this there has been a tendency to regard their diagnosis as impossible clinically owing to the wide variety in their presenting symptoms and the absence of any pathognomonic signs or symptoms. There is indeed a so-called "classical story" but its features are presented more frequently by tumours situated elsewhere, and too often when, in its absence, the diagnosis has not been considered, a colloid cyst is subsequently revealed by ventriculography. The recent description by Bull and Sutton (1949) of pathognomonic ventriculography findings in these cases does not, however, absolve the clinician from all responsibility. It is indeed most important that any tendency to regard a condition as clinically undiagnosable merely because in the past ventriculography has proved more reliable must be discouraged, and this for two reasons: the first being that many of these cases have no definite signs of raised pressure in the early days, when they are first seen in the consulting room, so that unless the condition is suspected ventriculography will never be given the opportunity to prove itself. A second cogent reason is supplied by a consideration of Case XI in this series. Ventricular drainage was undertaken as the first stage in the treatment so as to allow the patient to recover sufficiently to undergo ventriculography. Had the diagnosis been considered, and indeed in this case there was little enough to suggest it, unilateral ventricular drainage would never have been contemplated: ventriculography followed by radical surgery would have been applied at once, with possibly happier results. It is indeed because of the special dangers of the condition that neurologists should attempt to learn as much as possible about the clinical behaviour of these cysts so that they may answer accurately the two questions so frequently arising, "Is there a tumour present?" "If so, is it one that should be dealt with urgently?" Repeatedly among the reported cases one reads of the patient

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dying suddenly—a tragedy when the cause of death is a benign removable tumour (Grossiord, 1941, and Shaver, 1940).

It is the writer's belief that failure in the past to make an accurate diagnosis more frequently in this condition is mainly due to a misconception of the common mode of evolution of the clinical picture. The following cases, many of which have been previously recorded, are here reported in detail[1] in an attempt to analyse the symptoms and signs, the object being to determine whether these have a characteristic pattern and sequence and, if possible, to establish a clinical syndrome which may encourage clinical neurologists in the future to make the diagnosis with greater accuracy.

Dandy (loc. cit.) stated that it was impossible to diagnose this condition with certainty on clinical grounds alone, and later writers have emphasized this (Grossiord, 1941; Bull and Sutton, 1949). Nevertheless, the increasing accuracy of our mechanical aids to diagnosis, by impressing our mistakes on us earlier and with greater emphasis, should assist us to improve our clinical judgment rather than encourage us to abandon clinical study.

The Classical Story

The story that we have been led to expect is one of intermittence—a story of paroxysmal attacks of headache, with vomiting and amblyopic attacks—often followed by loss of consciousness, prolonged coma, or with profound mental changes, and later complete recovery, and remissions lasting even up to years. The headache in particular is characterized by sudden onset, with increasing intensity, working up to a crescendo; there is a strong postural factor, sudden movements of the head tending to induce a rapid onset of headache, others causing instant relief of the pain. Such is the classical story (Dandy, 1933, and Grossiord, 1941). Examination, however, of the following cases shows that in these at least it is an uncommon story, whilst careful study of the case notes of a series of 361 consecutive tumour cases at the National Hospital reveals that most of its features can be produced by tumours in various other situations. The present paper is an attempt to show that there is a common pattern, not so distinctive or striking as the classical story, but one which, when all its aspects are present, should lead to a reasonably confident clinical diagnosis when all the evidence available prior to ventriculography has been sifted.

Material

Twenty-nine cases are here reported, all of whom were proved, either at operation or at autopsy, to be suffering from a colloid cyst of the third ventricle. Of these 29 cases, 20 were cases that were admitted to the National Hospital, Queen Square. 2 cases were admitted to the Maida Vale Hospital for Nervous Diseases,

[1] Cases I–XIV, Bull and Sutton, 1949; Case II, Jefferson, 1937; Case III, Jefferson and Jackson, 1939; Cases XXIII, XXV, and XXVI, Bull and Sutton, 1949.

and 7 were admitted to the Atkinson Morley Hospital. The cases were subsequently operated upon by Professor Jefferson, Mr. Harvey Jackson or Mr. Wylie McKissock.

Study of the following case reports, and careful analysis of the cases reported in the literature, reveal that these cases may present in one of three ways:

(1) As a simple problem of localization in a patient complaining of headache alone, and on examination showing bilateral papilloedema and no other abnormal signs with the possible exception of the common false localizing signs.

(2) As a progressive or fluctuating dementia with or without headache, and with or without the signs of raised pressure only.

(3) With a strong history of paroxysmal attacks and with complete freedom from all symptoms in between.

The analysis also reveals that the most frequently repeated symptom, apart from headache, appears to be sudden weakness of the lower limbs, causing falling without loss of the senses.

Case Histories[1]

Case I.—A. H., male, aged 31. Admitted to the National Hospital on April 4, 1936, under Sir Charles Symonds. Complained of occasional headaches for four months, "A heavy feeling, or a downright terrible ache" across the forehead and at the back of the eyes, more right than left; occasionally commencing as a sudden terrific pain in the right eye lasting seconds only and followed by the slight heavy ache, lasting thirty minutes. Headaches were worse if up and about, and eased by lying in bed. Three weeks before admission while riding his bicycle he experienced a sudden headache and was nauseated: he dismounted, was assisted to a house and promptly vomited. He recovered by the next day and had since experienced nausea only. He admitted to certain vagaries of memory but no other symptoms. On examination his intelligence was recorded as average, V.A.R. was 6/12, V.A.L. was

[1] *Case Reports.*—Note the correlation between these cases and the previous reports on them in the paper by Bull and Sutton (1949) is as follows:

This series	*Bull and Sutton*
Cases I–V	Cases I–V
Cases VI–VIII	Cases XII–XIV
Case X	Case XV
Case IX	Case XVIII
Case XI	Case XVII
Cases XII and XIII	Cases XIX and XX
Case XIV	Case XXIV
Case XVIII	Case XI
Case XIX	Case X
Case XX	Case VIII
Case XXI	Case VII
Case XXII	Case VI
Case XXIII	Case XVI
Case XXIV	Case IX
Cases XXV and XXVI	Cases XXII and XXIII

Cases XV, XVI and XVII, and XXVII–XXIX have not previously been reported.

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6/9: there were three to four dioptres of papilloedema on both sides, and the left pupil was very slightly irregular. There was a fine tremor of the outstretched fingers on both sides, and on testing stance there was a tendency to fall backwards.

Special investigations.—X-ray of the skull was normal: cerebrospinal fluid (C.S.F.) (examined at another hospital): Pressure 300+, one cell, 55 mg. of protein per cent, negative Wassermann reaction (W.R.) and normal Lange curve. Ventricular fluid contained ·01 mg. of protein.

Eight days after his admission before any surgical intervention had taken place he suddenly lapsed into unconsciousness. A ventricle was tapped, followed by a right subtentorial decompression by Mr. Harvey Jackson. He never recovered his senses and he died the same day. At post-mortem (Dr. Greenfield) a massive, acute infarction in the territory of both posterior cerebral arteries was discovered. On opening the lateral ventricles there was bilateral hydrocephalus and on removing the fornix a rounded, pale green ball-like tumour was found attached to the tela choroidea. The tumour consisted of colloid in which were embedded the remains of cells and nuclear fragments.

Case II.—M. R., female, aged 45. Admitted to the National Hospital under Dr. Macdonald Critchley. Seven years before admission she started to suffer from attacks of transient weakness of the legs. Her legs would suddenly become weak, and give way so that unless supported she fell to the ground. Both legs were equally affected. Between attacks her gait was unaffected but she also complained of periodic feelings of faintness. At the same time as the onset of these symptoms she began to express paranoid ideas that she was being watched by people who thought that she was a communist spy, that she was being poisoned and that the cartoons in the papers had personal sinister meanings. On account of the mental disorder she was admitted to the Maudsley Hospital in July 1929 and she remained there for sixteen months. In the Maudsley notes it was recorded: "At first she was stuporose and resistant: she had one attack of headache and vomiting followed by an attack of loss of consciousness (it is not recorded how long this attack lasted but it was followed by tingling and paralysis down the left side). In May 1930 her mental and physical condition was much improved but it was noticed that there was bilateral papilloedema that may have been present earlier." It was considered that the diagnosis was that of cerebral tumour but that her mental state showed no organic features, and she was discharged in November 1930. At the time of her discharge from hospital she was considered much improved, mentally clear, but there remained an occasional tendency to complain that people were looking at her, and to be depressed. However, she continued to complain of frequent severe headache, vertico-occipital in distribution, often accompanied by vomiting, of periodic attacks of momentary blurring of vision and of the attacks of falling to the ground without loss of senses. Six months later she had one attack of loss of senses, accompanied by "Irregular movements of the arms and legs, and by ? voiding of urine"; this attack lasted one hour. There then followed a period, two years in duration, during which she lived in Italy, and throughout which time she was in perfect health apart from occasional headache and the same attacks of falling previously described. Three years before admission to the National Hospital, on the day she returned from Italy, she experienced a very severe headache for several hours accompanied by vomiting; she then suddenly shouted and fell to the ground unconscious. Clonic movements of the arms and legs were observed, she voided urine and the attack lasted thirty minutes. Following this attack she was very weak and unable to leave her bed for three days, while for the succeeding three weeks she suffered from frequent severe headaches and a severe depression. There then followed six months of complete freedom from all symptoms. In the following six months five major epileptic seizures occurred and frequent headache so she was readmitted to the Maudsley where she remained for six

months: steady improvement occurred while in the hospital, the headaches became progressively less severe and frequent and the papillœdema was observed to subside. She was discharged in November 1934, readmitted in December for re-examination and no change in her condition was noted. In the following ten months she remained well, complaining only of fatigue and occasional headache. Finally, four months before her admission to the National Hospital she again started to complain of frequent severe vertico-occipital headaches becoming progressively more severe, and occurring every day. After two months of this she had a severe bout of constant headache lasting two days and again at the end of this time suddenly lost consciousness and a major fit occurred. On this occasion consciousness was regained in ten minutes but for the next few days many fits a day occurred and she complained of constant severe headache: she slowly slipped into a condition of semi-coma; her rapid demise was anticipated, the relatives were summoned but she again recovered after two days; she gradually became clearer mentally but three days later, on her admission to the National Hospital, she was bewildered yet able to supply a clear account of her illness. On examination it was noted that her intelligence was normal apart from a pronounced memory defect for recent events and defective orientation in time and space. Visual acuity was 6/36 right and 6/24 left: two dioptres of papillœdema right and one dioptre left with atrophy of the disc. There were no other abnormalities in the cranial nerves. She was unable to stand without support, and swayed in all directions, her gait was strongly ataxic and she tended to lurch in all directions. Rapidly alternating movements were poorly performed by the upper limbs especially on the left side; there was a moderate hypotonia of the lower limbs, a moderate symmetrical, general reduction in muscle power, and a gross inco-ordination of the lower limbs of a type associated with cerebellar disease. The deep reflexes were present and equal apart from the left ankle-jerk which was absent. Both plantar responses were extensor.

Special investigations.—C.S.F.: Lumbar pressure 260 mm. of water; one cell, 55 mg. of protein per cent, and Wassermann reaction negative. X-ray of skull demonstrated almost complete erosion of the posterior clinoid processes. A clinical diagnosis of tuberculoma in the posterior fossa was made, the correct diagnosis was made at ventriculography and Professor Geoffrey Jefferson removed a typical colloid cyst, the size of a small cherry, at craniotomy. The patient recovered.

Case III.—G., H., female, aged 52. Admitted to the National Hospital under the care of Dr. Hinds Howell on September 25, 1936. Five months before admission she suddenly and unaccountably fell to the ground while walking. Her legs suddenly crumpled up under her but there was no loss of consciousness or feeling of faintness or vertigo. Her husband noticed she was pale. A week later the same occurred again, and in the next four months there were countless similar attacks always exactly the same. Fourteen days after this first attack she suddenly left her bed in the middle of the night, for no reason that she was subsequently able to recall and abruptly lost her senses and fell to the ground. It was observed that both sides of the face twitched in this attack but there was no movement of arms or legs and no incontinence of urine or biting of the tongue. For the following week she complained of continuous, severe, frontal headache, equal on both sides and she repeatedly vomited on attempting to eat. After the end of this week she suffered only occasional mild frontal headache and was sick once only. Right from the onset of the illness her husband noted mental changes which were more marked following upon her single attack of loss of consciousness. He noted first a failure in her interest in events, later a progressive dulling of her intellect: for four months she had been unable to look after her household, she became obsessional about the necessity to have more money, was always asking for it and refused to pay her bills. For two to three months she had been disorientated, subject to false ideas about a stream of imaginary visitors, suffered from delusions and false

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ideas about her monetary possessions. Her memory for recent events deteriorated and whereas previously she had been depressed, she became happy and placid, with a ready smile, and a tendency to minimize her complaints, to refuse to admit to incapacity although she had been confined to her room for four months. Her gait became slow, and unsteady with a marked tendency to fall backwards. On examination she was found to lie motionless in bed, "A lethargy so marked that she appeared to be in danger of falling out of bed without making any effort to save herself." She was drowsy, disorientated in time and space, and had no insight. There was a marked memory defect. Her mood was placid and attention poor. Visual acuity was 6/24 right and 6/18 left and there was bilateral papillœdema of two dioptres. There was a moderate degree of plastic extra-pyramidal type of rigidity of the right arm and leg involving both flexors and extensors equally. Deep reflexes were present and equal and the left plantar response was weakly extensor. She was incontinent of urine and fæces.

Special investigations.—C.S.F.: Lumbar pressure 300+ mm. water; no cells; 35 mg. of protein per cent. W.R. negative. X-ray of skull revealed no abnormality. Ventriculography was performed by Mr. Harvey Jackson on 11.9.36 and a ventricular drain was set up. Following this no change in her condition was noted but she died suddenly seven days afterwards without any further operative intervention or any change in her condition to suggest deterioration. The ventriculographic changes were typical and the diagnosis confirmed at autopsy.

Case IV.—A. G., male, aged 36. Admitted to the National Hospital under the care of Dr. J. St. Clair Elkington on March 6, 1939. Four months before admission he started to suffer from headaches lasting ten minutes at a time and occurring three or four times daily. The headache was bilateral and symmetrical, frontoparietal in distribution. He described the headaches as dull pains with occasional sharp throbs; though never unbearable they could be fairly severe; they occurred any time of the day; there were no known precipitating or aggravating factors; they were uninfluenced by straining, coughing or sneezing. He had vomited on one occasion only and on that occasion the headache was different: it was right frontal in distribution and exceptionally severe: it lasted for three days and he vomited throughout this period. Occasionally during the attacks of headache his vision blurred; the upper half of his field of vision blacking out momentarily. On reflection he stated that he could recall an exactly similar attack of headache, lasting five days, fourteen years previously. When the headaches were very bad he occasionally noticed a rhythmic fluctuating buzzing noise in the right ear. On examination his mental state was normal. Visual acuity was 6/6 in both eyes, there was moderate bilateral papillœdema and the right pupil was larger than the left, it reacted poorly to light, the range being small and the contraction poorly held. Both pupils reacted well on accommodation-convergence, the left rather better than the right. There were no other abnormal physical signs.

Special investigations.—C.S.F. (at another hospital): Pressure 300 mm. water; no cells; 20 mg. of protein per cent. W.R. negative. X-ray of skull demonstrated erosion of the posterior clinoid processes. Ventriculography revealed the typical features of a colloid cyst and Mr. Harvey Jackson performed a craniotomy and removed the cyst on 24.3.39. The patient recovered.

Case V.—W. H., male, aged 42. Admitted to the National Hospital under the care of Dr. F. M. R. Walshe on September 16, 1939. For three months he had complained of attacks of "dizziness." A typical attack was as follows: When cycling along a road he suddenly found himself being irresistibly forced over to the right: he then dismounted and sat down and within three minutes he was able to proceed again, symptom-free. Accompanying this attack there was a headache localized to the frontal region, but no further details were supplied about these headaches. At the onset he suffered only occasionally from these attacks but later they were occurring two to three times a day. Should he be walking

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when the attacks commenced, he tended to stagger, again to the right, but only for a matter of fifty yards. In recent weeks the headaches had been more severe, generalized and affecting, in addition, the back of the neck. They were not associated with change of posture, but straining tended to initiate the headaches and they were often accompanied by vomiting. On examination his mental state was normal. Visual acuity was 6/10, and there was early papillœdema on the left side only. The deep reflexes were thought to be slightly brisker in the right upper limb than the left. It was recorded that when walking his head was slightly rotated with the chin to the left and the occiput towards the right shoulder. There were no other abnormal physical signs in the nervous system and the blood pressure was 120/80.

Special investigations.—C.S.F.: Pressure was 210 mm. water; two cells and 60 mg. of protein per cent. W.R. was negative. X-ray of the skull showed some slight flattening of the sella turcica. Ventriculography revealed the typical appearances of a colloid cyst and Mr. Julian Taylor removed the cyst at craniotomy. The patient recovered.

Case VI.—E. W., female, aged 39. Admitted to the National Hospital under the care of Mr. Harvey Jackson on May 14, 1946. Originally she had been admitted to another hospital in 1945 with a history extending over "some years" of periodic intense headache; vomiting and attacks of loss of senses were features of these headaches and a diagnosis of migraine was made; the appearance of her discs being regarded as those of pseudopapillœdema, in spite, apparently, of a lumbar C.S.F. pressure of 220 mm. water. Later, in 1945, she was admitted to another hospital where a history was obtained of headache that had occurred ever since childhood, lasting a day at a time. Twelve years previously these headaches became sufficiently incapacitating to make her have to stop work for a day (she was a domestic). The headaches were temporal, extending across the forehead and the backs of the eyeballs felt sore and tender; they were always relieved by lying down, were usually accompanied by vomiting, sometimes preceded by a complete blacking out of her vision for a few seconds, sometimes by lights dancing in front of her eyes. These headaches continued at frequent intervals until two years before her admission to the National Hospital, since when they had been more frequent, less intense, almost invariably preceded by tingling in the face, at first the left side only, but later both sides. On examination, in 1945, no abnormal signs were noted and the optic fundi were regarded as normal. Skull X-rays showed no abnormality and an E.E.G. showed some 6 c/sec activity in both parietal regions. C.S.F. pressure was again 220 mm. water. She was discharged from this hospital and for six months was free of symptoms. However, the attacks of pins and needles over the left side of the face then recommenced with some differences. After a few moments the pins and needles sensation would develop into an aching pain around the left eye and temple and within a short time the entire left side of the face felt as though it had been injected with cocaine. The numbness persisted for a few minutes and then gave way to a burning sensation. She also started to suffer from severe headaches lasting from five to thirty minutes, frontal and associated with vomiting that relieved the pain, and occurring, as did the attacks of pain in the face, twelve times a day. The onset of both sorts of attacks was sudden; rising from a chair frequently started an attack. During a headache her knees would shake and twitch and she would feel as though she would fall if she did not sit down, but apparently she never did fall. The vision in her left eye sometimes failed during the headaches. On examination at the National Hospital her intelligence was regarded as normal. Vision was 6/6 right and 6/9 left. There was chronic bilateral papillœdema of 3½ dioptres. The left corneal reflex was absent and there was slight inco-ordination of the right arm.

Special investigations.—Skull X-rays showed expansion of the pituitary fossa and erosion of the clinoid processes. Mr. Harvey Jackson performed a craniotomy

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on 17.5.45 and removed the cyst but she died four days later from hæmorrhage into the ventricles.

Case VII.—N. H., male, aged 31. Admitted to the National Hospital under the care of Dr. Purdon Martin on 7.5.47. He had first noticed diminution in the vision of the right eye only nine months previously. The failure, as far as he was aware, affected the whole of the field of vision at the same time and it was slowly progressive so that by the time he was first seen at an out-patient consultation by the writer, the eye was virtually blind. Vision of the left eye was unaffected. At the same time as he was aware of the failing vision he noticed a "muzziness" of the head and occasional fleeting mild pain in both eyes. He commenced to suffer from real headaches about a month before admission; a muzzy feeling in the occiput, coming on gradually at the end of the day and only then if he had been working hard (he was a clerk); it lasted for two hours, was associated with a red hot feeling in the eyes and lying flat used to cause instant relief of the headache. There had been no vomiting, fits, attacks of falling, intellectual deterioration or personality change. On examination there was no evidence of intellectual deterioration. Visual acuity was down to hand movements only at three feet on the right, 6/6 left. There was bilateral papillœdema of two dioptres with several hæmorrhages scattered about both retinæ. The visual fields demonstrated a nasal defect on the left with a general constriction of the right field, the greatest sparing of vision being in the lower nasal quadrant (*see* note). There were no other abnormal physical signs.

Special investigations.—C.S.F.: Lumbar pressure was 300+ mm. water; no cells; 25 mg. of protein per cent. W.R. was negative. X-ray of skull revealed no abnormality, and a ventriculography revealed the typical appearances of a colloid cyst. Mr. McKissock performed a craniotomy and removed the cyst. The patient recovered.

Case VIII.—F. C., male, aged 40. Admitted to the National Hospital under the care of Dr. F. M. R. Walshe on July 28, 1947. He started to suffer from headache two years previously: the pain commenced suddenly on VJ Day and recurred with increasing frequency until in the five weeks prior to admission when it had been constantly present. The pain was bi-frontal, was at first not severe and lasted about an hour, but latterly it had been so severe as to put him off work and his wife frequently found him "banging his head in agony"; the pain was throbbing in character, he had to lie down but this did not relieve it; there was photophobia and nausea, with occasional vomiting and occasionally the headache had been preceded by the appearance of white rings that appeared to move about in front of his eyes, blurring the vision and lasting about thirty minutes. The headache occurred at any time of the day and was relieved by compound aspirin tablets. Four months prior to his admission he was suddenly incontinent of fæces while walking to work: there was no reason for this, no alimentary upset and apparently no interference with his state of consciousness at the time. The same occurred one month later under the same circumstances. In the last few weeks his memory had been deteriorating, concentration had been poor, he frequently yawned and had been depressed and tearful for no adequate reason. On examination he was slightly retarded and apathetic. Visual acuity was 6/6: when the writer first saw this patient in the out-patient department there was a suspicious blurring of the nasal margin of both optic discs, right more than left, but there was no measurable swelling; this appearance was more marked three weeks later when he was admitted. There were no other abnormal physical signs.

Special investigations.—Skull X-ray showed marked thinning of the pituitary fossa and decalcification of the sphenoidal ridge on both sides. C.S.F.: Lumbar pressure was 250 mm. water; one cell 20 mg. of protein per cent. W.R. was negative. The E.E.G. showed no abnormality. Ventriculography revealed the

characteristic appearances and on 14.8.47 Mr. McKissock coagulated the cyst. The patient recovered.

Case IX.—I. H., female, aged 45. Admitted to the National Hospital under the care of Sir Charles Symonds on September 10, 1947. The story began five years previously when she suddenly fell to the ground for no reason, without any interference with her consciousness. She fell backwards and was able to rise again immediately and continue walking. Following this she continued to fall in this way, always backwards, two to three times a week. There was never any warning that it would happen but she always suffered from a headache after the fall that lasted all day; a severe, dull, throbbing, occipital ache, that frequently caused nausea, followed by vomiting that usually relieved the pain. In between attacks of falling she was symptom-free. In the past year she had lost all bladder control and been continually incontinent. In this year there had also been a progressive disability in her gait. Her legs had seemed to be weak, clumsy but not stiff and for the past three months she had been unable to walk at all without assistance; she had also deteriorated mentally, lost interest in the house, forgotten things that she had done an hour previously, and occasionally had appeared drowsy. Originally an active successful business woman, she had degenerated into an apathetic, careless, untidy simpleton, and she did not mind. On examination she was found to be drowsy, apathetic, indifferent to her incontinence, a reluctant but good-humoured historian with poor attention, yet able to give a reasonably good account of the progress of her illness. There was a demonstrable deterioration on psychological testing but she was able to complete more tests correctly than she could be bothered to attempt without persuasion. Visual acuity was 6/12 on both sides uncorrected, but the optic fundi were normal and the visual fields full. She was unable to sit up unaided, there was a moderate weakness of all muscle groups of both lower limbs, the abdominal reflexes were absent, knee and ankle jerks brisk, brisker right than left, and both plantar responses were extensor. She was unable to stand without support and fell backwards; on attempting to walk she demonstrated a complete inability to put one foot in front of the other; she seemed unable to initiate any of the movements required for walking, indeed she did not seem to know what to do with her legs at all.

Special investigations.—C.S.F.: Lumbar pressure was 160 mm. water; no cells; 20 mg. of protein per cent. W.R. negative. X-ray of the skull showed no abnormality. Ventriculography revealed a symmetrical hydrocephalus with an obstruction at the foramina of Munro. This was wrongly interpreted as being evidence of an inoperable lesion in the floor of the third ventricle and she was discharged to await deep X-ray therapy. However, soon after her discharge on 11.9.47 she rapidly recovered, discovered she could walk, at first with assistance and later by herself; her mental state improved but the falling attacks and incontinence of urine continued. She decided that there was no need to undergo deep X-ray therapy, but two months later her difficulty with walking slowly recurred, she suffered from a severe occipital headache lasting a week, but always relieved by lying down: so she was readmitted. On examination she was found to be completely immobile in bed, not caring to move to assist the nurses in their routine attentions. She was fatuous and had no insight. There was still no disc œdema and the signs were exactly as they had been before. Again there was the same discrepancy between a mild spastic paraparesis and a complete inability to carry out the movements that compose gait.

Special investigations.—The E.E.G. showed occasional brief outbursts of moderately high voltage 2 c/sec waves that were bilateral and symmetrical, in phase in all leads, and with the highest amplitude anteriorly. X-ray of the skull was normal. Ventriculography showed the characteristic appearances of a colloid cyst and on 15.4.48 Mr. McKissock removed the cyst. The patient recovered.

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Case X.—J. H., male, aged 41. Admitted to the National Hospital under the care of Dr. Denis Brinton on February 26, 1948. He was unable to give any details of his history himself: his wife supplied the following:

Whilst in the Army between 1941–45 he had several sudden attacks of loss of consciousness with falling: they lasted a few seconds only, there were no convulsive movements and no sequelæ to these attacks. For three years he had been free of these attacks. In addition he used to suffer from severe, hammering, frontal headaches, not accompanied by vomiting and from which he had also been free in the past three years. In this last three years there had been instead a progressive dulling of his mental faculties. From being an energetic, lively man, a conscientious worker, an interested father, he had become slow, lethargic, disinterested and unreliable. He went home only to sleep. Fourteen days before admission he lost his job. Temper, character, manner and pride in appearance had all changed for the worse. For twelve months the left arm had been noted to be slow and clumsy and he tended not to use it even for eating. His gait had become slow and uncertain. On examination there was a mild intellectual deterioration. Visual acuity was 6/6 on both sides, there was early bilateral papilloedema that had not been present a week previously when seen in out-patients. There was a slight left-sided facial weakness on voluntary contraction only; the left hand fell away quickly and, to a lesser degree, the left leg with corresponding weakness: the deep reflexes were slightly brisker left than right with preserved abdominal reflexes and an equivocal left plantar response, the right being flexor. Blood pressure was 135/85. His general appearance and manner was described as "Retarded and a little fatuous, suggestive of dementia paralytica in his countenance and way of turning to his wife to have the questions set him answered."

Special investigations.—C.S.F.: Lumbar pressure 240 mm. water; no cells; 30 mg. of protein per cent. W.R. negative. X-ray of skull showed slight ballooning of the sella and thinning of the dorsum. The E.E.G. was normal. Ventriculography revealed the characteristic appearances of a colloid cyst and Mr. McKissock removed the cyst at craniotomy. The patient recovered.

Case XI.—K. L., male, aged 35. Admitted to the National Hospital under the care of Dr. Michael Kremer on March 25, 1948. Seven days prior to admission he started to suffer for the first time from severe frontal headaches of a throbbing and expanding type, accompanied by feelings of unsteadiness, nausea and vomiting: these aches lasted thirty minutes at a time. Each day the headaches were more severe than those the day before, he became drowsy and had himself noticed that his mind seemed to wander. Unfortunately no other details are available. On examination there was a bradycardia of 48, a lateral nystagmus on vertical gaze, no papilloedema and no other abnormal physical signs. On account of his decreasing pulse rate and the fact that soon after admission he slipped into coma, a unilateral ventricular drain was set up, the clinical diagnosis being that of a posterior fossa tumour. Skull X-rays had demonstrated no definite abnormality. At the operation the lateral ventricle was found to be dilated, but following the procedure his pulse-rate rose rapidly, his pupils became dilated and fixed and he died within a few hours. At post-mortem the dura was found to be tense, there was moderate bilateral, tonsillar herniation and slight bilateral uncinate and hippocampal herniation. There was marked hydrocephalus of lateral ventricles and a small colloid cyst 1·2 cm. in diameter was found lying between the foramina of Munro and attached to the fornix. There was some petechial hæmorrhage into the tegmentum of the pons.

Case XII.—E. H., male, aged 38. Admitted to the National Hospital under the care of Sir Charles Symonds. Five months before admission he started to suffer from slight, momentary attacks of giddiness several times a day. "It was as if I were spinning around in a circle." At the same time, but independent of

these attacks, there were attacks in which a film appeared to come over the left eye for a few seconds. A few days after the onset of these symptoms he commenced to suffer from early morning headache, usually an hour after he had started his postman's round; a dull ache, above and behind both eyes, but accompanied by nausea or vomiting and lasting three to four hours. The headaches became so severe he had to take a week off work and for three months after this he was free of headache. Five weeks before admission he suddenly developed a splitting headache one afternoon in the usual situation and this remained continuously present for the succeeding five weeks, but it did not interfere with sleep. A few days after the onset of this pain he discovered that if he turned his head suddenly he experienced a severe, transient sensation as though he were spinning around, together with a transient weakness of the knees and followed immediately afterwards by transient blurring of vision in the left eye only. On two occasions in the last four weeks his legs suddenly lost all power: "While I was sitting in a chair I suddenly said: 'Well, I must be going now,' and slapped my knees with my hands. Immediately both lower limbs became so weak that I was unable to rise, and they persisted like this for some ten minutes." On examination there was a mild intellectual deterioration. There was bilateral anosmia; visual acuity was 6/9 right and 6/12 left. There was moderate left-sided papillœdema, but the right optic disc was flat although the veins were engorged. His blood pressure was 130/80. There were no other abnormal physical signs.

Special investigation.—X-ray of the skull was normal. The E.E.G. showed "A normal symmetrical record." Ventriculography revealed the characteristic appearances of the cyst and on 5.8.48 Mr. McKissock removed the cyst at craniotomy. The patient recovered.

Case XIII.—J. L. C., male, aged 34. Admitted to the National Hospital under the care of Dr. Denis Williams on August 6, 1948. Nine years previously he had experienced one unheralded attack of loss of consciousness at work. There were no witnesses to this attack, no biting of his tongue or voiding of urine. On recovering consciousness he was confused and unable to recognize workmates or relatives and he remained confused, weak and nauseated with occasional vomiting for a week. For the subsequent four years he was entirely symptom-free, and for the next twelve months he was subject to monthly attacks in which he would suddenly "feel a queer, numb, dead feeling: a lifeless strange feeling that I cannot describe better," associated with severe frontal headache, more right than left, and continued retching and vomiting lasting twelve hours each time. For a further six months he was free of symptoms and then these attacks recurred, but the headaches were more severe and lasted several days, with short-lived sudden aggravations of the pain. In addition, he commenced to suffer from irregularly occurring attacks of loss of consciousness without an aura. There were no convulsive movements, he was flaccid when unconscious, did not bite his tongue, nor void his urine. Again there was a six months' remission and for the last three years prior to admission there were periods of bouts of headache and "fainting turns" alternating with periods of well-being. Nine months before admission his vision started to fail and he suffered from visual blackouts in the right eye only, lasting several minutes. For years there had been a mild progressive memory loss and failure of concentration. On examination his mental state was normal to rough tests: visual acuity was 6/36 right and 6/12 left. There was bilateral papillœdema right more than left. His blood pressure was 130/70.

Special investigation.—X-ray of skull was normal; E.E.G. was normal. Ventriculography: there was at the time some difference of opinion as to the interpretation of these films and so Mr. Harvey Jackson performed a Torkildsen's operation to relieve the hydrocephalus. Following this there was a subsidence of the disc œdema and his visual acuity improved to 6/18 right and 6/9 left.

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A month after his discharge in October he started to experience for a week repeated attacks of headache induced by rising suddenly from a sitting posture, or from stooping; a sudden, sharp, severe, shooting pain inside his head, lasting for a few minutes and followed by frontal pain for an hour: these headaches were always relieved by lying down. His wife noticed that during bouts of severe pain he was always talkative and his speech was not coherent. There was no change in his physical signs but the severe pains continued to recur and his vision to fail again. He was readmitted on 17.12.48. Ventriculography revealed the typical appearances of a colloid cyst and on 21.12.48 Mr. Jackson performed a craniotomy and removed the cyst. The patient recovered.

Case XIV.—F. K., male, aged 26. Admitted to the National Hospital under the care of Dr. S. P. Meadows on March 17, 1949. He was Polish and unable to supply many details. For three months he had complained of moderately severe generalized vertical headache, lasting thirty minutes at a time, and unaffected by postural changes. These occurred three to four times a week. A month after the onset of these headaches he started to vomit during the headaches: the vomiting was unheralded by nausea and projectile in type. A week before admission he had complained of "giddiness" but there was no sense of rotation. On examination he was alert and co-operative. There was bilateral chronic papillœdema with scattered retinal hæmorrhages. The blood pressure was 138/90. There were no other abnormal physical signs.

Special investigations.—X-ray of skull was normal. C.S.F. (examined at another hospital): Lumbar pressure was 300+ mm. water, "contents normal." E.E.G.: "There was widespread fast activity at about 28 c/sec sometimes reaching an amplitude of 40 micro-volts, and frontal in origin. There was a low voltage normal alpha rhythm, and a few low voltage waves at about 6 c/sec. Significance was doubtful. Ventriculography revealed the typical signs and at craniotomy Mr. McKissock removed the cyst. It is of interest that in addition 30–40 c.c. of chronic subdural hæmatoma was encountered and evacuated from the right side in the process of ventriculography. The patient recovered.

Case XV.—R. C., male, aged 27. Admitted to the National Hospital under the care of Sir Charles Symonds on June 9, 1949. He complained of a moderately severe, bilateral headache for the past nine weeks only. It occurred immediately after leaving bed in the morning on every third day and lasted fifteen minutes. After five weeks of this there was a fortnight's complete freedom of symptoms but in the last fourteen days prior to admission the headaches returned but more frequently, more severe, occurring at any time of the day, and they were frequently precipitated by bending forward and relieved by extending the head or lying down. There was no nausea, no other symptoms and in between the headaches he was fit for anything. He was first seen in the out-patients' department of another hospital by Sir Charles Symonds and during the interview the headache occurred. Sir Charles Symonds was immediately impressed by the obvious dramatic onset of headache in a person who at one moment was perfectly fit and capable of describing his symptoms in a fairly happy-go-lucky style, and who quite suddenly changed colour, started to perspire and was obviously in great pain. There was no papillœdema and there were no abnormal physical signs but a provisional diagnosis of a tumour in relation to the ventricular system was made. A week later he was admitted to the National Hospital when early bilateral papillœdema with a few small flame-shaped retinal hæmorrhages were observed. There were no other abnormal physical signs and the blood pressure was 130/80.

Special investigations.—C.S.F.: Lumbar pressure 300+ mm. water; no cells; 45 mg. of protein per cent. X-ray of the skull was normal. E.E.G. was within normal limits. Ventriculography revealed the characteristic findings of a colloid cyst and on 25.6.49 Mr. McKissock evacuated and coagulated the cyst. The patient recovered.

Case XVI.—I. R., female, aged 26. Admitted to the National Hospital under the care of Dr. M. J. McArdle on October 12, 1949. For two years, occurring two to three times a day and nearly every day she had experienced brief visual black-outs lasting two to three seconds: recently these had been more frequent and were often induced by stooping. For one and a half years she had been subject to headaches of intense severity, always starting in the left temple, shooting up to the vertex in paroxysms lasting a few seconds and recurring every few seconds with ever-increasing severity until they were intolerably violent. She had on six occasions lost consciousness for several minutes when the pain was at its peak: this occurred about one hour after the onset of the headache, and always in bed to which she had been forced to retire by the pain. The attacks were never characterized by convulsive movements or tongue biting but on two occasions she voided urine. Occasionally the headaches were not so severe, lasted thirty minutes and were relieved by lying down: they invariably occurred in the late evening. Headaches occurred once a month but she had had none in the last three months. In the six months prior to admission her legs gave way so that she fell on three to four occasions. "They felt funny for five to ten minutes" and then suddenly gave way. There was no alteration in her state of consciousness and power was almost normal immediately afterwards. In the last seven weeks the vision of the right eye rapidly failed over the course of one week. On examination she was found to be of low intelligence with a mild memory defect. Visual acuity was 6/6 left but she was unable to distinguish light from dark on the right side. There was a moderate bilateral chronic papillœdema, more right than left with consecutive atrophy of the discs. The right pupil was dilated and reacted very slightly to light but briskly on accommodation-convergence. Blood pressure was 115/80.

Special investigations.—X-ray of skull showed marked thinning of dorsum sellæ, and marked beaten silver appearance of vault. E.E.G.: "In the occipital regions there was a rather irregular alpha rhythm at about 9 c/sec overshadowed by more generalized activity at about 6 c/sec tending to occur in runs and by more isolated slower waves. No focal abnormality. The record suggests raised intracranial pressure." Ventriculography revealed the characteristic appearances of a colloid cyst and Mr. McKissock evacuated and cauterized it at craniotomy. The patient recovered.

Case XVII.—N. B., male, aged 26. Admitted to the National Hospital under the care of Sir Charles Symonds on January 4, 1950. For three months he had complained of mild headaches above the left eye becoming more severe, persistent and widespread and occurring in two bouts each lasting a week during which the headache would persist for twelve hours. Headaches were frequently accompanied by nausea and retching and movement of his head always caused a superadded throbbing element. Since the last attack, three weeks previously, there had been a mild frontal headache more often present than absent. For one and a half months vision had been misty especially in the mornings and most marked in the left upper quadrant. On six occasions he had experienced attacks of sudden onset lasting twenty seconds in which he felt light headed and his vision clouded over; recovery was immediate and there was no falling. In addition there had been several attacks lasting about one minute when his legs, particularly his knees, felt as if they did not belong to him. There was no falling. On examination there was no intellectual defect. Visual acuity was 6/6, there was moderate bilateral papillœdema, with one hæmorrhage on the left disc. There were no other abnormal physical signs.

Special investigations.—X-ray of skull: the dorsum and floor of the sella was a little ill-defined suggesting raised intracranial pressure. E.E.G. was symmetrical, contained a regular alpha rhythm and in all areas moderate voltage 4–7 c/sec activity which was increased symmetrically by overbreathing and associated then

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with some slower waves. This was considered to be abnormal and consistent with raised pressure with no localizing features. Ventriculography revealed the typical appearance of a colloid cyst, but with only a moderate degree of dilatation of the ventricles. Mr. McKissock performed a craniotomy, evacuated and cauterized the cyst. The patient recovered.

Case XVIII.—B. C., male, aged 35. Referred to Mr. McKissock by Dr. Feiling and admitted to the Atkinson Morley Hospital on January 19, 1946. Eleven years previously he had experienced a single attack of headache preceded by a brief spell of misty vision and hyperacusis and accompanied by blacking out of all the vision except for a narrow patch of preserved vision in the centre, and by zig-zags of light across this patch. The headache passed after two tablets of aspirin. For ten years he was free of symptoms. He then commenced to suffer from a different sort of headache, a severe, heavy, clinging ache, generalized, lasting fifteen minutes at a time, relieved by caffeine, and occurring at first once a week, and later more frequently and mostly first thing on leaving his bed, in the evening (he was on night work). During these headaches, and at no other time, he experienced queer feelings in both arms and legs which he could not describe precisely: the left side was affected by sensations of pins and needles, his legs trembled and he felt generally weak. There was no nausea or vomiting. Nine months before admission he was suddenly and unaccountably incontinent of urine once only. Two months before he noticed a falling off of his mental powers. One week before admission he experienced a sudden attack of headache while walking home, his legs were suddenly so weak that he had to sit down on a doorstep, and for a brief spell he lost awareness of his surroundings. On recovering he continued his journey but discovered that his vision had deteriorated so that he was unable to read newsprint and his vision remained blurred. On examination there was bilateral papilloedema of five dioptres and no other abnormal physical signs.

Special investigations.—X-ray of the skull showed enlargement of the sella, ventriculography revealed the characteristic appearance of a colloid cyst. Mr. McKissock performed a craniotomy on 21.1.46 and attempted to remove the cyst. The patient died seven days later and at autopsy death was found to be due to hæmorrhage into the basal ganglia.

Case XIX.—M. C., female, aged 25. Referred by Dr. Walshe and admitted to the Atkinson Morley Hospital under Mr. McKissock on December 7, 1945. She had complained for two years of very severe but short-lived headaches of an occipital and retrocollic distribution. These headaches were caused or aggravated by straining or violent exercise and always relieved by lying down or by bringing the head forward. Occasionally these headaches were accompanied by nausea, blurring of vision and diplopia. As the headaches became more severe her gait tended to be slightly unsteady, and her memory, she thought, was deteriorating. There had been no attacks of falling or of loss of senses. On examination her mental state was considered to be normal. Visual acuity was 6/6 both sides and there was moderate, bilateral papilloedema. There were no other abnormal physical signs.

Special investigations.—C.S.F. (examined at another hospital): Lumbar pressure 300+ mm. water. There were no cells, 30 mg. of protein per cent. W.R. was negative. X-ray of her skull showed erosion of the posterior clinoid processes. Ventriculography revealed the characteristic appearances of a colloid cyst. At craniotomy Mr. McKissock removed this cyst but the patient died three days later. At autopsy hæmorrhage into the basal ganglia was discovered.

Case XX.—L. M., female, aged 26. Referred by Dr. J. St. Clair Elkington and admitted to the Atkinson Morley Hospital under the care of Mr. McKissock. There was a past history of one illegitimate pregnancy ending in a still-birth, followed by three pregnancies each terminating in a premature infant that did not

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survive and two pregnancies terminating in a normal delivery. Her husband was under treatment for general paralysis of the insane. She had complained of headache for four and a half years, which for the first four years was a dull, heavy, parieto-occipital headache, equal on both sides, accompanied by a sensation that the head "wanted to fall backwards and to the right," and occurring at six-monthly intervals. In the final six months these headaches had been short-lived, had occurred every day, had been accompanied by nausea and by momentary episodes of complete loss of vision. For twelve months she had been aware of a continuous buzzing noise in the left ear, which she could arrest by pressing her fingers immediately behind the pinna of that ear, or by turning her head to the left. She had been subject to curious attacks in the last six months which commenced with dyspnœa, rapidly followed by a swimming feeling and hissing noises in the head, succeeded in turn by a vigorous shaking of the right hand which rendered it useless. Then the right leg started to shake in a similar fashion, her teeth chattered and the attack would subside without there having been any clouding of consciousness. The whole lasted ten minutes and occurred frequently. For three months there had been a slight progressive weakness of the right arm and leg. On examination her mental state was normal, there was bilateral papillœdema and a doubtful right facial weakness. There were no other abnormal physical signs.

Special investigations.—C.S.F.: Lumbar pressure 110 mm. water; no cells; 10 mg. of protein per cent. W.R. negative. X-ray of the skull showed thinning of the dorsum sellæ. Ventriculography revealed the characteristic appearance of a colloid cyst and at craniotomy Mr. McKissock removed the cyst. The patient recovered.

Case XXI.—E. R., male, aged 48. Referred by Dr. Wilfred Harris, and admitted to the Maida Vale Hospital under Mr. McKissock on September 10, 1942. He had complained for twelve months of unusual attacks, occurring frequently, and usually lasting five minutes which commenced with a feeling of faintness and giddiness, followed by a simultaneous, symmetrical, clonic jerking of both arms and legs. The clonic movements continued for two minutes and during them he was fully conscious, knew where he was and what was happening but was unable to make voluntary movements or speak. Very occasionally consciousness was lost. On one occasion he was left immobile and speechless for a day following an attack. The only known precipitating factor was alcohol. In addition and for the same period he had suffered from headache about once a week, frequently immediately preceding or following an attack; a severe ache on the left side of the head lasting ten minutes only. On examination his mental state was normal; there was early bilateral papillœdema and no other abnormal physical signs.

Special investigations.—C.S.F.: Lumbar pressure was 220 mm. water. X-ray of skull was normal. Ventriculography revealed the characteristic appearances of a colloid cyst and at craniotomy Mr. McKissock removed the cyst. The patient recovered.

Case XXII.—H. A. W., male, aged 50. Referred by Professor Golla and admitted to the Maida Vale Hospital under the care of Mr. McKissock on January 2, 1939. Six months before his admission and for a period of six weeks only he suffered from weekly attacks of pain. The pain began in his right forehead, passed down the right side of his face, neck and trunk, to the outer side of the right leg and foot. The attacks lasted only two to three seconds, were not severe, but were followed by a slight numbness of the affected foot that impeded his walking for five to fifteen minutes afterwards. There was no permanent weakness or loss of sensation. For the last month he had noticed mistiness of vision and a frequent short-lived diplopia. Two days before his admission there was a sudden, unprovoked fit of weeping which was, for him, most unusual. On examination his mental state was

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normal, there was bilateral papillœdema with retinal hæmorrhages, and no other abnormality.

Special investigations.—X-ray of skull and E.E.G. were normal. Ventriculography was interpreted as indicating a posterior fossa lesion and Mr. McKissock performed a posterior fossa decompression. The patient died shortly afterwards and the diagnosis was made at autopsy.

Case XXIII.—A. E., male, aged 42. Admitted to the National Hospital under the care of Mr. McKissock on February 9, 1948. He started to suffer from headaches three years beforehand: a pressure type of occipital pain with a pain "like knives" shooting through both eyes, lasting two to five minutes, accompanied by a sensation as though he would faint and relieved by sitting down and putting his head back. After eighteen months he was free of headache for six months but at the time they stopped the right arm rapidly lost its power so that after three days he was unable to move it on account of weakness and pain at the large joints: finger movements were spared. This condition remained static for two months and then improved so that after a further three months the arm was normal. The headaches reappeared in the final twelve months, in the last three of which they were much more severe, occurred two to three times a day and accompanied by the sensation that the ground was moving from under his feet, and the right foot gave way so that he fell to the right. The attacks still lasted two to three minutes, were still stopped by lying down, and were accompanied by blurring vision. On examination there was chronic bilateral papillœdema and consecutive atrophy; an irregular central scotoma was observed in the right visual field, and there were no other abnormal physical signs.

Special investigations.—X-ray of skull was normal. Ventriculography revealed dilatation of both lateral ventricles and a bilateral Torkildsen's operation was performed by Mr. McKissock. There was no improvement, myodil ventriculography suggested but was not diagnostic of a colloid cyst and at craniotomy Mr. McKissock removed the cyst. The patient died a week later.

Case XXIV.—L. C., male, aged 29. Referred by Dr. J. St. Clair Elkington and admitted to the Atkinson Morley Hospital under the care of Mr. McKissock on November 3, 1944. Nine months previously he had started to suffer from attacks in which his left leg suddenly became weak and he was unable to move it either at knee or ankle: he had to hold himself up, the weakness persisted for an hour, was accompanied by a fuzzy feeling in the head but at the end of each attack he recovered completely. Attacks occurred nearly every day and on three or four occasions the left wrist was similarly affected with the leg, while later still, both legs were affected at the same time. Two months before admission he was suddenly seized with a violent headache between the temples and was sick: the left leg lost its power but after sixty minutes recovered though the headache persisted. Later that day the left leg again became weak and he was aware of a sound of flowing water in both ears and a sensation that both eyes were bulging out of his head. He recovered that night. A month later a violent thumping headache came on, he vomited intermittently for three hours, felt stone cold and perspired profusely. Following this he had no further symptoms. On examination there were no abnormal physical signs in the nervous system.

Special investigations.—C.S.F.: Lumbar pressure was 280 mm. water; no cells, 30 mg. of protein per cent. X-ray of the skull was normal. He was discharged, his symptoms became less severe, for six weeks he was entirely well and then headaches reappeared, but this time they were very violent, left-sided, occipital pains accompanied by nausea and vomiting, and momentary loss of vision: they lasted minutes only but were very frequent. Three weeks before readmission on 6.11.45 a severe headache lasted two days and was associated with a twilight state during which he was incontinent and for which he had afterwards complete amnesia. On examination there were again no abnormal physical signs. Ventriculography

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revealed the typical appearances of a colloid cyst and Mr. McKissock removed this at craniotomy. The patient recovered.

Case XXV.—M. F., female, aged 43. Admitted to the Atkinson Morley Hospital under Mr. McKissock on December 14, 1948. For six years she had complained of frequent, severe, bifrontal headaches, of sudden onset, lasting ten minutes at a time, and relieved by lying down. In the past twelve months they had been less frequent and more severe. For four years there had been a gradual deterioration of vision and for the same period there had been attacks of rotatory vertigo of sudden onset frequently causing her to fall and lasting thirty minutes at a time. For one year she had suffered from attacks of sudden loss of senses occurring about once every three weeks and lasting from three to one hundred and twenty minutes. In these she lay flaccid on the ground, there were no convulsive movements, or biting of the tongue. She was occasionally incontinent of urine either just before or at the end of these attacks. Eight days before admission she was admitted to another hospital because of the rapid development of coma. At that time she demonstrated constricted, circular, fixed pupils, bilateral papillœdema, and a left extensor plantar response. Within one and half hours she had recovered consciousness, a lumbar puncture revealed a pressure of 150 mm. water only, 3 cells and 25 mg. of protein per cent. On examination on admission to the Atkinson Morley Hospital she was found to be drowsy, retarded, indifferent and at times facetious: She was incontinent of urine and fæces. There was bilateral papillœdema: visual acuity was 6/18 right and 6/24 left. There was a minimal weakness with increased reflexes on the left side, yet she was unable to stand, and at attempts to stand, stood on a wide base and slowly fell backwards and to the right: on attempting to walk she overbalanced because her feet would not follow her body.

Special investigations.—X-ray of the skull showed signs of raised pressure only, E.E.G.: There was a diffuse bilateral abnormality, rhythms of upwards of 7 c/sec occurring generally. Ventriculography revealed the characteristic appearances of a colloid cyst and at craniotomy Mr. McKissock removed the cyst. The patient recovered.

Case XXVI.—M. D. C-B., male, aged 40. Referred by Dr. Sandifer and admitted to the Atkinson Morley Hospital under the care of Mr. McKissock on March 16, 1949. Three weeks previously he started to suffer from parieto-occipital headaches of increasing severity. At first there was a dull background of headache with paroxysms of suddenly increased intensity lasting fifteen minutes. For the last week the headache had only been present on waking in the morning. The headaches were accompanied by nausea and vomiting and there had been slight mistiness of vision. On examination his mental state was normal. Visual acuity was 6/4 right and 6/5 left. The fundi were normal, there were no abnormal physical signs and the blood pressure was 110/80.

Special investigations.—X-ray of skull was normal. E.E.G.: An unstable dominant rhythm was slow and arose far forward. The changes were widespread and symmetrical. It was considered that if the changes were due to raised pressure it was long-standing. Ventriculography revealed the characteristic changes of a colloid cyst and on 22.3.49 at craniotomy Mr. McKissock evacuated and coagulated the cyst. The patient recovered.

Case XXVII.—P. N., female, aged 23. Referred by Sir Paul Mallinson and admitted to the Atkinson Morley Hospital under the care of Mr. McKissock on January 4, 1950. For the previous three weeks only she had suffered from a persistent bilateral vertical headache of increasing severity and accompanied by stiffness of the neck, nausea and vomiting. In addition she had complained of transient noises in her head, of sudden onset and lasting two hours at a time "like hundreds of seagulls screaming." On four occasions her right elbow suddenly became stiff, so that she was unable to use the arm for thirty minutes. Since the onset there had

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been a gradual blurring of vision with transient diplopia. On examination her mental state was normal. An inconstant humming bruit was heard, only in the left frontal region and which was not affected by carotid compression. Visual acuity was 6/6 right and 6/12 left. There was marked bilateral papillœdema with exudates and a right sixth nerve paresis. There were no other abnormal physical signs apart from a doubtful increase in the tendon reflexes of the right side.

Special investigations.—X-ray of skull revealed erosion of the posterior clinoid processes. E.E.G. showed a rhythmic 4–5 c/sec wave occurring equally on both sides in episodes having quite high voltage. Ventriculography revealed the typical features of a colloid cyst and on 9.1.50 at craniotomy Mr. McKissock evacuated and coagulated the cyst. The patient recovered.

Case XXVIII.—R. S., female, aged 32. Admitted to the National Hospital under the care of Dr. S. P. Meadows on July 7, 1950. For three years she had suffered twice a week from aching pains in the forehead and temples lasting a few hours at a time. A year beforehand these became worse. On a background of dull aching pains, severe grinding pains of momentary duration appeared in both temples and shooting through her head. Lying down produced relief. She occasionally vomited and was also subject to brief attacks of flashing lights in one or other temporal field of vision either with or independently of a headache. The headaches had eased in the past seven weeks. There was no history of ataxia. On examination her mental state was normal. Visual acuity was 6/9 right and left. There was moderate bilateral papillœdema. There was a slow anti-clockwise nystagmus on right conjugate gaze with the head back. In the upright position there was in addition a quicker anti-clockwise nystagmus on left lateral gaze. There were no other abnormal physical signs and particularly no inco-ordination of the limbs or ataxia of the gait. Blood pressure was 150/90.

Special investigations.—X-ray of the skull: the sella was markedly enlarged and the posterior clinoid processes destroyed. E.E.G.: A symmetrical 8–9 c/sec. alpha rhythm was blocked by visual attention. 3–7 c/sec waves of medium voltage were often seen on the left, or the right side, the distribution being occasionally synchronous: there was no clear asymmetry. Ventriculography revealed the characteristic appearance of a colloid cyst and on 20.7.50 Mr. McKissock at craniotomy removed the cyst. The patient recovered.

Case XXIX.—M. H., female, aged 48. Admitted to the Atkinson Morley Hospital under the care of Mr. McKissock on August 4, 1950. She had been in excellent health until ten days previously when she developed severe vertical headache without nausea or vomiting. The headaches increased in severity; on the sixth day she became drowsy, on the seventh she slipped into a coma from which she never recovered. On examination she responded only to very painful stimuli: pulse rate was 80: the fundi were normal: the left pupil was larger than the right, and neither reacted to light. There was spasticity and no movement to stimuli of the left arm and leg while the left tendon reflexes were brisker than the right. The abdominal reflexes were absent and both plantar responses were extensor.

Special investigations.—C.S.F. (examined at another hospital) was under greatly increased pressure. X-ray of skull showed osteoporosis of the dorsum sellæ and decalcification of the floor of the middle fossa. Ventriculography: both lateral ventricles were dilated, the right considerably more than the left: the septum pelucidum was displaced and bowed to the left: no air entered the third or fourth ventricle but in one hanging head lateral view a dilated foramen of Munro could be seen. These were interpreted as being evidence of an expanding lesion of non-operable nature in the third ventricle and a bilateral ventricular drainage was set up. No improvement in her condition occurred after this and she died twenty-four hours later. At autopsy a colloid cyst was discovered occluding the third ventricle. There was a well-marked medullary pressure cone.

An Analysis of the Presenting Symptoms

(1) *Headache, papillœdema and no localizing features.*—As Dandy himself stated not the least reason for suspecting the presence of such a tumour is the complete absence of any localizing features (Dandy, 1933). It is undoubted that many of the cases previously reported presented as cases of cerebral tumour causing headache and vomiting and on examination papillœdema only. In this series no less than 11 out of the 29 presented this problem (Cases I, IV, VI, VII, VIII, XIV, XV, XVIII, XIX, XXII, XXIII). Three more of these cases (XIII, XVI, XVII) presented additional features, of no lateralizing value, but which in themselves might have suggested the diagnosis: two complaining of these highly significant attacks of temporary abrupt weakness of the knees (Cases XVI and XVII) and the third presented a remitting history (Case XIII). What, however, has never been previously established is how often other types of cerebral tumour present this very problem, what sort of tumours and what their site. In an attempt to establish this a survey of the clinical notes of all tumours proved at the National Hospital in the past two and half years, in all over three hundred, was carried out. It was also considered useful to determine what information was yielded by means of the ancillary aids to clinical examination prior to ventriculography in these non-colloid cyst tumours for comparison or contrast with that obtained in the colloid cyst series.

It was considered that these points were worthy of investigation because the writer finds it surprising how rarely in general up to now the diagnosis of colloid cyst is tentatively put forward in cases presenting in this way, and in fact, how rarely was it put forward in the cases under review that proved to have colloid cysts. Indeed in the past it has been more or less generally taught that cases that present with headaches, papillœdema and no localizing signs are usually discovered at ventriculography to be suffering from mid-line tumours, most commonly in the posterior fossa, with perhaps, cranio-pharyngiomata as the commonest supratentorial tumour. As will be shown the analysis of these tumours at Queen Square does not support this teaching.

Out of the series of 361 tumours, 21 cases were selected as presenting with this syndrome. These 21 were the only patients who had complained of headache only and no localizing symptoms (including true epileptic fits which are very rare in cases with colloid cysts) and who on examination had no true localizing signs, but the signs of raised intracranial pressure only. 14 of these patients were subsequently proved to have some tumour other than a colloid cyst.

Only 3 out of these 14 cases had tumours in the posterior fossa (out of a total of 49 posterior fossa tumours in the series). Of the remaining 11

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cases 2 were subsequently considered to have a thrombosis of the sagittal sinus: one proved to have tuberose sclerosis: and an additional 8, bringing the total including the case of tuberose sclerosis up to 9 had tumours localized somewhere above the tentorium cerebelli. Only one of these 9 had a mid-line tumour, and that was indeed a case of cranio-pharyngioma. All the others, as is shown in the accompanying table had tumours in one or other hemisphere.

TABLE I.—TUMOURS, ETC., PRESENTING AS CASES OF HEADACHES, PAPILLŒDEMA AND NO LOCALIZING FEATURES

Diagnosis	*No. of cases*	*X-ray report*	*E.E.G. report*	*C.S.F.*	*Any other features of diagnostic value*
Supra-tentorial:					
Tuberose sclerosis	1	Signs of raised pressure only	Non-specific abnormality	Not examined	Typical lesions on face
Meningioma temporal	1	Signs of raised pressure only	Not done	Not examined	
Meningioma frontal	1	Typical bone changes	Lateralizing features	Not examined	
Meningioma parietal	1	Signs of raised pressure only	Not done	Not examined	
Meningioma sphen. ridge	1	Signs of raised pressure only	Not done	Ventricular protein 500 mg. per cent	
Glioma frontal	1	Signs of raised pressure only	Lateralizing features	Not examined	
Secondary carcinoma multiple	1	Pineal shift	Lateralizing features	Not examined	
	1	Pineal shift	Lateralizing features	Not examined	
Cranio-pharyngioma	1	Signs of raised pressure only	Non-specific abnormality	Not examined	
Sub-tentorial:					
Mid-line meningioma of tentorium	1	Normal X-ray	Non-specific abnormality	Not examined	
Left cerebellar glioblastoma	1	Normal X-ray	Non-specific abnormality	Protein 120 mg. per cent	
Mid-line cerebellar glioma	1	Normal X-ray	Non-specific abnormality	Not examined	
Other cases: No tumour found					
Sinus thrombosis	2*a*	Normal X-ray	Non-specific abnormality	Normal	
	b	Normal X-ray	Non-specific abnormality	Normal	

In this series of over 300 tumours are included 11 of these cases of colloid cyst, of which 7 presented with headache, papillœdema and no

localizing features, and there was one more indeed (Case XII) whose only symptom of possibly localizing value was that of vertigo. Vertigo is such a common symptom and compatible with the presence of a tumour both above and below the tentorium and in any part of these two divisions that in carrying out this survey the writer regarded it as of no localizing value unless it were accompanied by some other suggestion of temporal lobe or posterior fossa localization. So it may be said that out of a total of 22 patients presenting the syndrome under discussion 8 proved to have colloid cysts (or if Case XII is to be discarded 7 out of a total of 21). That is to say one-third at least of these patients.

The ancillary aids to investigation in the cyst cases yielded no information of any value. The Electro-encephalogram (E.E.G.) was either normal or else it revealed a non-specific abnormality compatible with a degree of raised intracranial pressure and with no localizing features. Radiological changes in the skull were confined, as also one would expect, to the radiological signs of raised intracranial pressure. Arteriography is obviously not considered as a general rule when lateralization of the tumour is in doubt.

Of the 14 other tumours presenting in this way, some assistance was supplied by other investigations. Of the 3 posterior fossa tumours, one, suffering from a cerebellar glioblastoma had a high cerebrospinal fluid (C.S.F.) protein (120 mg. per cent). The C.S.F. was not increased significantly in any cases in which it was estimated in the cyst series, nor is a raised protein reported as a feature of the cases in the literature of this subject. Neither X-ray of skull, nor E.E.G., of these 3 posterior fossa tumours provided any help, the changes being those of a generalized raised pressure. Information of value was obtained by the usual aids in five out of the nine supra-tentoral lesions—sufficient at least effectively to rule out the diagnosis of a mid-line tumour. The correct diagnosis in the case of tuberose sclerosis was established by the presence of the facial stigmata. In the case of frontal meningioma there was a large frontal spur sufficiently characteristic to establish the diagnosis: the E.E.G. of the case of frontal glioma, and of the two cases of secondary carcinomatous deposits firmly and correctly suggested the correct side and lobe affected: the skull X-rays of the two cases of secondary carcinoma also revealed a significant shift of the pineal. There remains the one case of cranio-pharyngioma, which being a mid-line lesion could not be expected to produce E.E.G. changes of a specific nature, and the 3 other cases of meningioma, in none of which were there characteristic X-ray changes, and in none of which unfortunately was an E.E.G. recorded.

It can, therefore, be shown that by means of the commonly performed ancillary aids to diagnosis, the number of patients in which the site and

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side of the tumour was in doubt, was reduced to 16—and of these 16 cases no less than 8 proved to have colloid cysts in the third ventricle.

It would seem that these benign tumours were the commonest single cause of the clinical picture under discussion in this series of over three hundred cases. Furthermore, as a result of studying the skull X-ray, the E.E.G.s and the C.S.F. of all patients who had presented in this way, it may be concluded that the chances of any one of these patients having a colloid cyst in the third ventricle is about one in two. This diagnosis should, therefore, always be considered under these circumstances—and indeed, a return to the bedside and further questioning of the patient with this diagnosis to mind may lead to positive evidence—questions about the type of headache, the occurrence of attacks of falling and so on.

(2) *A fluctuating or progressive dementia.*—Grossiord (1941) discusses this type of presentation at length. In 14 of the cases he analysed there was a marked dementia, in some suggestive of a general paralysis of the insane, in the rest a syndrome similar to Korsakoff's syndrome was recorded. In one case only, reported by Foerster (1864) was the dementia fluctuating, and in two others (Paterson, 1935; Fulton, 1929), there was a story of transitory confusion and amnesia following upon the paroxysmal attacks of headache and analogous in Grossiord's view to the post-ictal state of an epileptic. It was Riddoch (1936) who first called attention to the fact that these cases may present with a profound progressive dementia even in the absence of headache and papilloedema. There can be little doubt but that the dementia observed is due to the considerable degree of hydrocephalus that is always present in these cases and so there is nothing about the dementia that one would expect to find that in any way differentiates it from a dementia following upon a hydrocephalus dependent upon any other cause. And, indeed, in the 6 cases in this series in which the degree of dementia was notable, this was the case (Cases II, III, IX, X, XI, XXV). The mental state of these 6 is indistinguishable from that which we are all accustomed to observe in large tumours of the frontal region or of the corpus callosum, or in cases of chronic hydrocephalus due to posterior fossa neoplasms. It was recorded of Case III, "She seems to be in danger of falling out of bed without making any effort to save herself. Such was her state of inertia. She is placid, contented, peaceful and maddeningly inattentive"; of Case X, "He is retarded and a little fatuous: there is a smooth G.P.I.-like countenance and a G.P.I.-like fashion of turning to his wife to leave her to answer the question." Of Case IX, "An active, successful business woman until three years ago, but marked deterioration has been noticed in the past year. She has lost interest, been indifferent, apparently happily unable to control her micturition—a reluctant historian, good-tempered, inattentive and disinclined to attempt things that she can manage with

ease." The notes on Case XI were very incomplete owing to circumstances, but it was briefly recorded that he had been drowsy, inert and tended to wander in the mind. These remarks could easily have been recorded about a host of patients with tumours invading the corpus callosum, with general paralysis of the insane, with any of the presenile dementias, or indeed of patients in the immediate post-leucotomy period. These are merely descriptive of the results of long-standing widespread, cerebral damage.

In one of these cases alone (Case II) was there a slightly different picture. It was considered at the time that her psychosis presented none of the features of an organic dementia and that it was entirely unconnected with her tumour. After her operation, however, she never presented herself again at the Maudsley Hospital or at the National and all attempts to trace her have up to now failed. It is, therefore, a matter of conjecture whether she has not returned to the Out-Patients' Department because removal of the cyst resulted in the removal of the underlying cause of the dementia, or whether failure to present herself, or be traced, is due to the fact that the progression of her psychosis resulted in her admission to some other hospital for mental diseases. It may, however, be significant that the occurrence of the first symptoms undoubtedly due to the cyst, that of transient weakness of the lower limbs, was accompanied by the first manifestations of the psychosis; that accompanying the paranoid psychosis was that curious mental state of mild stupor, inertia, and failure to co-operate, which improved concurrently with the improvement in her paranoia; that these manifestations fluctuated considerably with almost complete remissions; and that finally after re-entering that very same state of stupor, after being so comatose that the relatives were summoned as to the death-bed, she recovered within a few days to a state in which she was able to give a reasonably clear account of her illness. It is also recorded in the Maudsley notes that even at her most paranoid, she showed considerable fluctuations, being wildly deluded in the morning, by the evening she had regained complete insight into her delusion, yet may well be deluded the next morning. It would seem most likely that this was a case of a rather mildly paranoid woman, who, as a result of her intermittent hydrocephalus, presented a more florid picture associated with the more organic type of dementia and semi-stupor caused purely and simply by the greatly raised intra-ventricular pressure. And, indeed, that had it not been for the latter, her paranoia alone may never have brought her to psychiatric attention.

In Case III the mental changes were among the first symptoms, but they were rapidly followed by the typical attacks of sudden paresis of the lower limbs, by attacks of loss of consciousness and by headaches

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which were outstanding for fourteen days, but which afterwards ceased to be a prominent feature. In Case X the prominent early feature was the profound mental and personality change, followed much later by a disability affecting the left upper limb. In Case IX the mental changes came some years after the first symptoms, and were after that marked by very suggestive fluctuations. The writer recalls that her recovery was so outstanding that a diagnosis of intermittent obstruction was regarded as inescapable. She even recovered sufficient intelligence to refuse her deep X-ray therapy which subsequent events proved to have been incorrectly prescribed.

Of the series of 361 tumours at Queen Square, only 5 presented as a problem in localization owing to the presence of a progressive or fluctuating dementia with no well-defined localizing signs. 2 proved in the event to be suffering from tumours of the corpus callosum, one a large left frontal glioblastoma, one a bilateral subdural hæmatoma of at least two years' duration and with a strongly fluctuating story. The fifth had a large, subfrontal, mid-line meningioma; the localization of this latter was suggested by a bilateral anosmia, but there had been no history of headache, and on examination no papillœdema. Of the tumours, therefore, of this series of over three hundred tumours that presented this particular problem, 3 had cysts in the third ventricle (IX, X, XI), and 5 had other types of space occupying lesions, 2 of which proved to be operable. No conclusions can justly be drawn from a comparison of these figures, they are too small. They do, however, re-emphasize the well-established doctrine that the possibility of a space-occupying lesion must always be borne in the mind in the presence of a progressive dementia or personality change even in the absence of both headache and papillœdema and even with a comparatively long history; in addition that these space-occupying lesions have, in this series at least, been as frequently benign as not and that the possibility of their proving to be a colloid cyst in the third ventricle must always be kept well to the front, not necessarily because they are common, but because they are operable, curable conditions, among the host of distressingly incurable presenile dementias.

(3) *Cases with the "classical" features.*—As is explained on page 24, one is led to believe that typically there is a story that may be one of many years, or only months or weeks, in which there is a striking history of episodic attacks lasting a variable period but followed by complete remissions. In these attacks headaches of sudden onset may occur, headaches that can be relieved or aggravated strikingly by change of posture of the head: headaches that may be accompanied by visual disturbances, by vertigo, by transient pareses of the limbs, by alteration in the state of consciousness down to coma, or by marked mental changes. Grossiord

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makes a great point of the recurring story of episodic attacks of this nature and states that it was present in all but 12 of the cases published that he reviewed. He went even further and speculated that it may well have also manifested itself in those 12 but for the briefness of their history or the paucity of the clinical detail given by the author reporting the case (Grossiord, 1941). The writer does not consider that this assumption is really warranted in view of the small number in this series that produced a story that might conceivably be regarded as following the classical lines. Indeed, reading through the previously reported cases critically, one gains the impression that to describe the majority of these cases as providing a story of typical intermittence means accepting as such the sort of intermittent headache that is so commonly a feature of any type of intracranial neoplasm.

In this series Case XV suffered from headaches that were truly paroxysmal and it was the nature of these headaches, the suddenness of their onset, and their obvious intensity that suggested the correct diagnosis to the physician who saw him at an out-patient consultation. Apart from the attacks of falling, which the writer regards as highly suggestive in any case, the story of Case II is that of severe mental disturbance followed by apparent complete recovery. The presence of bilateral papillœdema was noted at least six years before the correct diagnosis was arrived at by means of ventriculography. Amblyopic attacks occurred throughout this period: there was, that is to say, a high degree of raised pressure throughout. Yet the effect on vision of this long-continued rise in intracranial pressure was merely to reduce the acuity to 6/24 and 6/36—a fact that suggests to the writer that the raised intracranial pressure could not have been due to a progressive expanding lesion which would surely have resulted in complete blindness not very many months after the onset of the amblyopic attacks, but was more likely to have been caused by intermittent pressure only such as in fact these cysts frequently cause. Apart from this, the story is one of remarkable fluctuation. It was recorded that six years prior to her admission to the National Hospital she was stuporose and resistant, vomiting, complaining of headache and it was known that she had bilateral papillœdema. Six months later she was much improved and mentally clear though still mildly paranoid at times. She tended to continue to suffer from periodic headache and amblyopic attacks but unfortunately the type of headache, its behaviour, and its relationship to the amblyopic attacks is not recorded. The attacks of transient paresis of the limbs continued. For the two years passed in Italy there was apparently complete relief of all symptoms apart from headache and attacks of falling. Three years before her admission to the National Hospital there was another sudden episode, characterized by severe

headache and vomiting, and loss of senses, followed by intermittent pain in the head for a few weeks, and again followed by six months almost entirely symptom-free. A few months later a series of attacks of loss of consciousness occurred accompanied by sufficient mental changes to warrant readmission to the Maudsley Hospital. During the subsequent six months her condition again improved together with improvement in her vision and for a further fourteen months she was again free of symptoms. Four months before admission, the headaches returned every day, the fits returned and she gradually slipped into the same semiconscious stuporose state that she had been in six years previously. She was so ill that the relatives were summoned, yet without any treatment directed towards relieving the raised pressure, she again improved. By the time she was admitted to the National Hospital she was quite accessible, and showed only a slight memory defect, bilateral consecutive optic atrophy and a bilateral ataxia, left more than right. It is worthy of note that it had been recorded at the Maudsley Hospital that the degree of papillœdema throughout this time had been noted to wax and wane considerably.

This is a story of very marked remissions. On account of the ataxia the tumour was clinically localized in the posterior fossa. Yet in retrospect it is not easy to visualize an expanding lesion in the posterior fossa that would behave in this way and yet produce so little in the way of permanent damage. Not easy, yet it must be admitted it is possible. The writer recalls a patient, who was admitted to the National Hospital under Sir Charles Symonds, whose history extended over thirty years, who had lost his sight at the age of 15 with a consecutive optic atrophy, and who had, in the succeeding years, passed through a series of brief periods when there had been an exacerbation of his symptoms with long intervals of comparative freedom from disability apart from his blindness, in between. At the age of 45 he came to the National Hospital during an episode of severe headache and increasing ataxia of two months' duration. He proved to have a calcified mass, probably a tuberculoma, in the posterior fossa. However, this was surely an exceptional case, and when, as so frequently happens, one's clinical diagnosis has to depend upon a balance of probabilities, a story such as that of Case II covering so many years during which the degree of papillœdema has been observed to fluctuate, associated with such marked fluctuation in the clinical state and with the significant attacks of transient pareses of the limbs, is highly suggestive of a diagnosis of intermittent ventricular obstruction.

Case IV complained of paroxysmal headaches over four months only, lasting ten minutes at a time, and occurring three to four times a day, but it was specifically noted that these headaches were uninfluenced by

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postural change; there was one episode lasting three days of persistent severe headache with vomiting and visual disturbance, and there was a significant story of a similar episode lasting only five days, fourteen years beforehand with complete freedom in between. There were no localizing features, but he had bilateral papillœdema and so it is felt that if the fourteen-year-old story is to be accepted as significant, as surely it must be, that combined with the absence of any localizing features, would place this case in the group conforming to the more traditional pattern.

Case XIII: His history commenced with an attack of loss of senses, followed by a period of seven days in which he was confused, weak and vomiting. Four years of complete freedom of all symptoms followed. Then there commenced a series of attacks marked by queer feelings, by frontal headache, and by retching and vomiting: these lasted at first about twelve hours, but later for several days. There were attacks of loss of senses, abrupt in onset and characterized by flaccidity of the limbs during the attacks. These were repeated over a period of six months and were followed by another year free of symptoms, and then a period of three years' duration in which periods of almost complete freedom alternated with bouts of headache and fainting. Once more there were no localizing signs, and it could fairly be said that his symptoms were comparable with the more classical stories recorded in the literature of cysts of the third ventricle.

Finally, in this connexion the story of Case IX can be considered. The original story on her first admission was that of a slowly progressive dementia and difficulty with walking, with attacks of falling: a history of five years' duration. There was, however, an almost complete remission starting within a month of leaving hospital and during which her mental processes became almost normal and she regained the ability to walk. This remission only lasted two months but it does make her total history partly comparable with the classical story. In this connexion, however, it must not be forgotten that it is not at all unusual for very marked improvement to take place in patients with cerebral tumours after a rest in hospital, even if no surgical intervention has been undertaken.

In this series of 29 cases, therefore, 2 (XV and II) presented a picture very similar to the classical idea of their behaviour, 2 (IV and XIII) were very suggestive, and a fifth (IX) had one suggestive remission that was rather more complete than is usually seen in tumour cases of such long duration.

However, in the series of 361 tumours analysed there were 8 that presented with stories that were, if anything, more reminiscent of the classical view of the behaviour of cysts of the third ventricle than any of the series of the 29 here reported. But 5 of these 8 had definite localizing signs, a sixth had radiological evidence of meningeal spur. Of the two with no

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localizing features, one had a mid-brain lesion blocking the aqueduct and the eighth had a left temporal glioma.

The tumours concerned proved to be as follows:

(1) Left, fronto-parietal, secondary carcinoma.
(2) Left, temporo-parietal cystic glioma.
(3) Left, temporal tumour, histology unverified.
(4) Cranio-pharyngioma.
(5) Bilateral cerebellar ependymoma.
(6) Right, frontal cystic glioma.
(7) Sub-frontal meningioma.
(8) Tumour of pineal region, histology unconfirmed.

These all presented with a story of marked remissions, with episodic headaches, headaches that were markedly provoked or relieved by postural changes. None of these features can be regarded as peculiar to intra-ventricular tumours, but can be caused by a variety of types of tumours in a variety of places. What is emphasized though by these tumours is the fact that it is the mid-line tumours which for the most part produce no localizing signs and that this sort of story, in the presence of papillœdema and in the absence of localizing signs is most likely to be the result of a cyst in the third ventricle.

Attacks of Falling Caused by Sudden Paresis of the Lower Limbs

In this series 6 cases complained of attacks of falling (Cases II, III, VI, IX, XII, XVI) and one of sudden weakness of the lower limbs without falling (Case XVII). In the 361 tumours investigated only 3 associated with some tumour other than a colloid cyst in the third ventricle presented with similar "drop seizures."

It is of course appreciated that these seizures occur frequently unassociated with any tumour pathology, and probably as an epileptic phenomenon. There can be little doubt that what the patient describes as "An attack of sudden falling" may arise as a result of several different mechanisms. After careful questioning of patients who complain of this type of attack, the writer is convinced that as an epileptic phenomenon they most commonly arise as a result of one of three mechanisms. Either the patient is in fact subject to frequent myoclonic jerkings: he has himself commented on the way his arms jerk, and, at rest, his legs in typical sudden and involuntary single movements. When, however, in the erect posture what he experiences is a sudden unexplained fall to the ground without any interference with his state of consciousness. Nevertheless, on analysis it appears that probably what happens is that a sudden myoclonic movement of one or other lower limb results in an abrupt loss of balance, with immediate recovery of power and the patient is able

immediately to rise from the ground. He remembers falling but is usually unable to explain why he falls. The more intelligent patient is, however, frequently able to recall that it is one or the other limb that has thrown him down. The writer has carefully studied a small defective child of 7 who had such frequent falls that he was unable to reach the end of the ward without falling at least once: it was apparent on observation that sometimes it was one leg, sometimes the other that threw him off his balance, and sometimes the whole trunk seemed to take part in a convulsive movement that almost seemed to cause the whole body to leap a few centimetres into the air, before collapsing. An intelligent young woman of 17 with similar drop seizures due to myoclonic attacks and whose mother had stated that the patient was subject to unexplained falls, was, however, able herself to explain the progress of events as follows, "I may be walking down the road talking to my friend when suddenly I seem to leap into the air quite unintentionally and when my feet touch the ground my legs collapse." In fact her feet never leave the ground, but so sudden and violent is the convulsive jerk that it is interpreted by her as a sudden leap into the air.

Secondly, there is a drop seizure that suggests a sudden inhibition of cortical activity. There is a sudden paresis of both lower limbs, apparently without any interference with his state of consciousness. The patient suddenly collapses to the ground and is usually unable to rise again for a few seconds because of the cessation of cortical motor activity. These patients claim that they fall suddenly, inexplicably, and are able to recall the actual process of falling.

Finally, the third and commonest of the three is a sudden brief attack of loss of senses that is sufficiently deep to cause the patient to fall, yet sufficiently brief for full consciousness to have returned before, or as he hits the ground: so that with these patients there is a story of sudden unexplained falls, that appear at first glance not to involve any interference with the state of consciousness because the patient is apparently able to recall falling.

When dealing with an intelligent patient it should be possible to "break down" any history of drop seizures and decide which of these three mechanisms are admissible for any particular patient. This may be of importance in deciding whether a history of attacks of falling is to be regarded as epileptic or as the result of some other mechanism associated with a tumour. Therefore the 3 tumour cases that were not colloid cysts and the 6 that were, were studied in an attempt to discover whether they in their history described anything that could justifiably give rise to a suspicion that they should not be regarded as simple epileptic phenomena—in other words whether a history of such attacks could alone

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support an out-patient decision to arrange for in-patient investigation should they be the only presenting symptom.

Of the cyst cases, Cases III and IX described sudden, abrupt falls, without loss of senses and with immediate recovery. Both were so vague and presented such a deterioration in their analytical powers that they were quite unable themselves to break down their sudden falls into a series of events. It may, however, be of significance that each presented a similar appearance of being unable to walk, of a tendency to fall backwards yet without there being sufficient demonstrable weakness or spasticity to explain why either of them had gone off their feet. Case XVI, however, commented that her legs felt "funny" for five to ten minutes prior to falling, and then "they gave way." Case XII described the attack as "My legs would become suddenly weak, as I was sitting: I would say, 'Well I must be going now,' slap my knees with my hands and then find that I was unable to move the limbs or rise: I would be like this for five to ten minutes." Case II, "While walking my legs would seem to become weak and give way under me, so that unless supported, I would fall." Case XVII, "My legs, particularly my knees, just felt as though they did not belong to me." Case VI would frequently feel that she would fall unless she sat down, owing to weakness of her legs; this only occurred when suffering from one of her headaches.

It would, therefore, appear that apart from Cases III and IX (about whom insufficient information is available), these are not true "Drop "Attacks" such as an epileptic would describe, but attacks in which the patient is aware of the fact that it is an actual weakness of the limbs that causes the fall because the duration of this paresis is sufficiently prolonged for the patients themselves to be aware of why they have fallen. In addition, in these attacks the patient is fully aware of his surroundings throughout these attacks. As was emphasized before, in the purely epileptic phenomenon the patients are rarely aware of why actually they have fallen: they do not ascribe the fall to weakness of the limbs, they merely record that suddenly and for no demonstrable reason at all they do fall.

Three further patients may be briefly commented upon at this stage who complained of similar symptoms but with variations that do not allow them legitimately to be included with these others. Case XVIII complained that only during the headaches he experienced queer feelings in both lower limbs which he was unable accurately to describe. The left leg was affected more than the right, both legs trembled and felt very weak, but they did not give way (not unlike Case VI), but on one occasion he had to sit down for fear of falling. Case XXIV, his first symptom was a sudden loss of power in the left leg only: he did not fall but "he was unable to move the leg from the hip downwards, and

the foot dropped." After resting he recovered completely but it was not a transient affair. These attacks were occurring every day and later the right leg was also involved. Case XXIII was liable to attacks lasting two to three minutes only in which his right leg only gave way with a tendency to fall to the right: the attacks accompanied headaches with blurred vision.

Of the non-colloid cyst tumour cases, the first described attacks of suddenly falling backward: no comment was made in the notes other than that these attacks were not accompanied by loss of senses: he proved to have a mid-line secondary carcinoma in the cerebellum and there were ample physical signs to site the lesion in the posterior fossa. The second stated, "My legs suddenly appeared to crumple up and I fell to the ground": there was no impairment of consciousness. An hæmangioblastoma in the vermis was confirmed by biopsy and on examination there was ample evidence of cerebellar defect. The third was a girl of 4 who suffered from typical drop seizures: the writer witnessed many of these attacks and he had no doubt that they were caused by a momentary loss of consciousness: she had a large parietal cystic glioma and the drop seizure was an epileptic manifestation.

There were, therefore, 6 cases among the 361 tumours of whom 4 had colloid cysts and 2 had mid-line tumours of the cerebellum who complained of what are best described as attacks of sudden paresis of the lower limbs without loss of senses; all 6 being cases that had grossly dilated lateral ventricles due to a block in the ventricular system. What is the mechanism of these attacks? This is obviously a question that is not open to a scientifically established answer. The attacks are too unexpected and brief to allow any electrophysiologic investigation into the mechanism during an attack. One can only theorize at the moment. For instance, in the presence of grossly dilated ventricles under pressure there may well be a critical level above which the capillary pressure in the brain is overcome, a temporary ischæmia results in a temporary blocking of impulses, not sufficient to render the patient unconscious but sufficient to cause an unexpected reduction in the power of the lower limbs and to precipitate the patient to the ground.

Headache

The accompanying diagram, Table II, is an analysis of the type of headaches described in an attempt to discover whether there is any recurring feature that in any way distinguishes them from the headaches frequently met with and due to other causes of a raised intracranial pressure. Unfortunately, in many of the case histories no record was made about the type of onset of the headache (whether sudden or gradual) or whether postural changes have any precipitating, aggravating or relieving effect upon these

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TABLE II

Case	Frequency	Duration	Situation	Sudden onset	Slow onset	Initiated by postural change	Relieved by postural change	Associated with other symptoms	Description of headache	Other symptoms accompanying headache	Amblyopic attacks	Length of history of headache
I	Occasional	30 min.	Frontal R. L.	+			+	+	A terrible ache across forehead, sudden terrific pain behind eyes	On one occasion nausea and vomiting		4 months
II			V.O. R. L.					+	Severe	Occasional vomiting, followed by loss of senses	+	8 years
III	Occasional		Frontal						Severe at first, later mild			5 months
IV	Two to four a day	10 min.	Fronto-parietal						A dull pain, occasional sharp aches	One attack persisted two to three days with vomiting and visual loss	+	
V	Two to three a day	2–3 min.	Frontal					+		Often vomiting		3 months
VI		5–30 min.	Temporo-frontal	+			+	+	Incapacitating	Vomiting, preceded by amblyopic attacks or hallucinations	+	12 years
VII	Occasional	2 hours	Occipital		+		+		A dull, nagging feeling, not severe			1 month
VIII	One to two a day		Frontal					+	Constant, subject to sharp exacerbations	Sometimes visual hallucinations or blurring	+	2 years
IX	Two to three a week	All day	Occipital	+				+	Severe, dull, throbbing	Follows attacks of falling and vomiting	+	
X	?	?	Frontal						Hammering, quite severe, none in last year			Indefinite
XI	?	30 min.	Frontal					+	Throbbing, expanding	Feeling of unsteadiness and nausea, vomiting. Bradycardia		7 days
XII	?	3–4 hours	Frontal						Dull ache, no nausea or vomiting. Lasts five weeks continuous			6 months

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XIII	One a month	12 hours	Frontal R. L.				A queer feeling, a dull pain	Retching and vomiting		5 years
XIV	Three to four a week	30–60 min.	Vault			+	Unable to speak English	Vomiting without nausea		3 months
XV	Every third day	15 min.	Frontal		+ +		Aching, quite severe with pallor of face			8 weeks
XVI	One a month	Secs.	Left temporal	+	+	+	Paroxysms of intense severity, recurring every few seconds, with increasing violence 30 m.	On six occasions lost senses at height of pain		6 months
XVII	In two bouts	1 day	Left eye fronto-occipital		+		Each bout lasted a week. Severe	Nausea and retching		3 months
XVIII	One a week	15 min.	Generalized			+	Heavy, clinging, severe	Queer feelings in arms and legs with weakness	+	1 year
XIX		Short-lived	Parieto-occipital				Very severe, sharp		+	2 years
XX	Six monthly every day	Short-lived	Occipito-parietal						+	4½ years
XXI	One a week	10 min.	Left parietal				Quite severe			12 months
XXII	One a week	2–3 secs.	Right head and face			+		Slight numbness right side of body		6 months
XXIII	Daily	2–3 min.	Occipital		+	+	Pressure type: later like knives	Dizziness and later loss of power in right leg	+	2¾ years
XXIV	Two a day	Hours	Bi-temporal	+		+	Violent	Nausea and weakness in left leg		2 months
XXV	Frequent	10 min.	Frontal	+	+		Severe			6 years
XXVI	One to two a day	15 min.	Generalized	+		+	Constant background of dull ache, with sudden paroxysms of intense severity	Nausea and vomiting		3 weeks
XXVII			Vertex			+	Severe and constant	Vomiting and tinnitus		3 weeks
XXVIII	Two a week	Hours	Fronto-temporal			+	Aching pains as background with momentary severe grinding paroxysms	Sometimes preceded by fortification spectra		2¾ years
XXIX			Vertex				Severe			10 days

L = Left ; M = Minutes ; O = Occipital ; R = Right ; V = Vertical.

headaches. This is a great pity as much is made about these features in the previously published case reports. In only 2 of this series (Cases XV, XVII) did the patient state that movement of the head was liable, and then not always, to induce a pain, and in only 3 others was it stated specifically not to do so (Cases V, VIII, XIV). Alteration of the position of the head was stated to relieve the pain in 8 cases (Cases I, VI, VII, XV, XVI, XIX, XXIII, XXV). The significant feature about this relief of pain on change of posture is that in all 8 cases the relief of the pain was produced by lying down. It is commonplace that usually the opposite happens in tumour cases, whereas it is just what one would expect might well happen when the cause of the raised pressure is an obstruction at the foramen of Munro caused by a colloid cyst.

A second point of interest is that in 16 of the cases the duration of the headache is recorded as being measured in seconds or minutes, and in Case XXVIII, although the headache lasted hours there were paroxysms of sudden increase in intensity lasting seconds only. It is obvious that it is not justifiable to claim that this is a feature specific to colloid cysts, as patients with other types of space-occupying lesions also occasionally complain of similar short-lived headaches; but not frequently. Over half the cyst cases of this series (16 out of 29) did so, yet only 9 cases out of the total of 361 cases of all other types of tumours recorded a similar story. In 4 of these the tumours were situated in the posterior fossa; of the remaining 5, one had multiple secondary deposits, scattered about the hemispheres, the second had a left fronto-parietal secondary, the third a temporo-parietal glioma, the fourth a sub-frontal meningioma and the fifth was due to an aneurysm of the posterior communicating artery. This type of short-lived headache can occur with most types of space-occupying lesions in most of the common situations, but it is worthy of comment that they occur more often than not if a colloid cyst is present, and that in our series of 361 tumours 13 patients complained of such headaches and 4 of these 13 proved to have colloid cysts.

Situation of the headache.—In the majority (16 cases) the situation is recorded as bilateral frontal, fronto-parietal or fronto-occipital. In the remaining it was mainly vertical or vertico-occipital.

Onset.—In only 5 cases was it specifically recorded as being of sudden onset and in 2 more there were sudden paroxysms of increased intensity, but many others are recorded as "short-lived," and must therefore have been of sudden onset. In only one case was the point emphasized that the headache was not of sudden onset.

Type of headache.—There seems to be nothing specific about the patients' description of their pain that differs in any way from the pain provoked by other tumours, except perhaps, that it does frequently appear to be described in terms suggesting great severity. Nausea and vomiting

accompanied these headaches rather more commonly perhaps than is usual (in 14 out of 29).

A feature that appears to the writer to be of much greater significance than any so far mentioned is a story of sudden loss of senses at the height of a headache. This is not common, and occurred only twice in this series (Cases II and XVI), but it is a story frequently encountered in the previously reported cases (Grossiord, 1941, *varia*), and only once encountered when studying the 361 case records: that one case was our own Case XVI, and had a colloid cyst. Though uncommon the writer feels that when this story does occur it has considerable diagnostic value. While it is true that stories of attacks of loss of consciousness are common enough in the histories of hemisphere tumours, these are epileptic manifestations, seldom preceded by headaches whereas in the attacks we are now describing there is headache that works up to a crescendo of pain—followed after perhaps hours, by the abrupt loss of consciousness.

In conclusion then it may be said that there is no outstanding pathognomonic feature about the headaches described in this condition. But it can fairly be stated that a number of features occur rather more frequently in association with colloid cysts than in association with tumours localized elsewhere, and that therefore a combination of several of these features might reasonably suggest this diagnosis. Such features are shortness of duration of each individual headache, relief of pain on lying down, a frontal situation, an intense hammering severity, perhaps working up to a crescendo of pain, accompanied by nausea and vomiting and terminating in an abrupt loss of senses—with long intervals of freedom from the headache in between.

Attacks Involving Loss of Consciousness

Eight of the patients of this series suffered at some time or another in the course of their illness from attacks involving the loss of their senses (Cases II, III, VI, X, XIII, XVI, XXI, XXV). In only 2 of these, however, is there a clear cut story of epileptiform fits (Cases II and XXI). Of the remaining cases too little information is available to allow any comment to be made about Case VI. "He is said to have lost his senses on more than one occasion, and vomiting occurred." For the others it is either a story of abrupt loss of senses with the patient lying flaccid and unconscious for a few minutes (Cases III, X, XIII, and XXV) followed by a varying period of headache, or a story of severe headache leading up to an abrupt loss of senses when the headache is very severe (Cases II and XVI). In no less than 41 of the cases analysed by Grossiord (1941) some sort of attack involving some clouding of senses occurred. In 29 of these there was complete loss of senses and the circumstances are in every way similar to the attacks described by the patients in this series,

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except in so far as Grossiord states that a varying period of headache, mainly in the region of thirty minutes, always preceded the attacks. In only 3 of the cases analysed by Grossiord was there a clear-cut story of epileptiform convulsions.

It would therefore appear that the incidence of undoubted fits is rare in these cases. But in a number of cases, roughly a third, there can be obtained a story of attacks (usually brief) of loss of senses, with flaccidity during the period of unconsciousness, and with a distinct relationship between the headache and the attacks, again not a story confined to this type of tumour, and therefore not in itself helpful towards the diagnosis. It would seem that these attacks are not due to epileptic discharges but they could rather be regarded as attacks of inhibition of consciousness possibly related to sudden increases in the degree of intracranial pressure. It seems likely indeed that the same mechanism is involved as causes the attacks of pareses of the lower limbs without loss of senses: in the latter the ischæmic effect falling mostly on the pyramidal tracts, in the former of a temporary blocking of all the impulses afferent and efferent occurs. It seems unlikely that these attacks, or the falling attacks, are due to any specifically local activity for they occur most frequently either in this condition or in mid-line posterior fossa tumours; the only common feature being the symmetrical hydrocephalus.

Endrocrine Changes

As Grossiord (1941) established signs referable to damage to neighbourhood structures such as the floor of the third ventricle have never been reported as a feature of these tumours. The writer is obviously unable to make definite statements about those cases in this series which he had no opportunity to interview. However, 11 of the patients in the series were personally interviewed by the writer, 4 before and after operation (Cases VII, VIII, IX, XII,) and 7 after operation (Cases X, XII, XIV, XV, XVI, XVII, XXVIII). The patients were directly questioned about the menstrual cycle, sleep rhythm, sexual life, water intake and output and temperature regulation. No evidence suggesting interference with these functions was obtained. It will be noted that in none of the cases in which the tension was recorded was there any hypertension. As the diagnosis was made at ventriculography only in the majority of these cases, it is obvious that the opportunity to carry out biochemical estimations such as blood sugar curves on the patients did not arise.

Anomalous Cases With Signs Falsely Suggesting a Localization

Three patients complained of vertigo (Cases V, XII, and XXV). This is a small number in view of Grossiord's statement that it was a symptom that occurred in 19 cases of his series. In Case V the vertigo was accom-

panied by an ataxia and a sensation of propulsion to the right: headache accompanied the vertigo and the attacks lasted a few minutes only: the physical signs supported a diagnosis of posterior fossa neoplasm. Cases XII and XXV suffered from spontaneous attacks of true rotatory vertigo while that in Case XII had been provoked by sudden movement of the head. There were no localizing signs in either but Case XII did complain of the attacks of falling: it is felt that vertigo in the absence of supporting physical signs must be regarded as of no localizing value.

One patient (Case II) was noted to demonstrate a gross ataxia of gait and a gross cerebellar type of ataxia of the lower limbs, at the time considered to be evidence of cerebellar involvement.

One patient (Case III) was considered to show extra-pyramidal type of plastic rigidity of the right arm and leg, and Case XX described attacks (which were not witnessed by any responsible observer) during which the right hand and later the right leg shook: it was considered at the time that these were possibly Jacksonian attacks but the physicians were not certain about this point, and the recorded description is not typical: the writer has not unfortunately had an opportunity of seeing this patient. One patient (Case XXI) complained of attacks that were said to be epileptic but it will be noted that although these so-called "clonic movements" of arms and legs involved both sides of the body simultaneously, there was no interference with his state of consciousness throughout, although they were followed by a variable period of inertia and speechlessness, without amnesia for any of the attacks. It seems doubtful whether these can be classified as true fits. Case XXVII had described a tinnitus of sudden onset lasting two hours at a time, "like hundreds of seagulls screaming." On examination, besides the papillœdema, there was an inconstant humming bruit audible only in the left frontal region, and consisting of a number of noises at different pitch. This must have been due to the hydrocephalus but the constant localization to one spot was misleading. Case XXVIII demonstrated a marked, constant rotatory nystagmus, anti-clockwise in direction and faster on conjugate deviation to the left: there were no other signs suggestive of cerebellar involvement.

Four other cases (X, XX, XXV, and XXIX) presented with moderate unilateral pyramidal signs.

These anomalous signs were sufficient to distract the clinician's attention and led to a false clinical localization. In retrospect it is felt that these signs could not have been ignored and therefore in these 9 cases an accurate localization on clinical grounds was impossible; however, it is worthy of comment that in spite of the nystagmus (which led to a primary diagnosis of a left cerebellar neoplasm) a secondary diagnosis of third ventricular cyst was made in Case XXVIII prior to ventriculography, following the principles laid down in this paper.

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Cases Presenting Without Papillœdema at Their First Attendance

On examination normal fundi were observed in 8 cases on their first attendance. It is, however, of interest that although only one of these 8 (Case VIII) had undoubted physical signs of central nervous involvement, and one other undoubted sign of mental deterioration, there was some feature in the story of all 8 sufficient to persuade the neurologist who saw them to arrange for their urgent admission as cases of cerebral tumour. The writer considers that these cases illustrate well how necessary it is for the clinician to bear in mind the principle that a diagnosis of psychogenic headache should be made only if there is positive evidence that the patient is liable to suffer from a neurosis. The description that Case XV gave in the out-patient department of his headache led the physician who saw him to make a firm diagnosis of a mid-line ventricular tumour, Case X demonstrated a type of dementia that is only seen in organic disease, Case XXIV complained of violent headaches of twelve months' history. There were three important, suggestive features in his story: the account of sudden pareses of his limbs, attacks of loss of vision during the headaches, and the inexplicable incontinence of urine on several occasions. The feature of greatest interest appears to the writer to be the fact that this patient described these momentary attacks of loss of vision at the height of a headache; this type of amblyopic attack due to a raised intracranial pressure must be unusual in the absence of a severe degree of papillœdema and is perhaps suggestive of a very sudden increase in the pressure from the normal rather than an increase in a chronically raised pressure. Case VIII was originally first seen by the writer in an out-patient consultation. He described a type of headache that is most frequently associated with psychological disorder and one which had been constantly present for many months. However he had the appearance of a sick man with a stable personality, so he was admitted to hospital with the presumptive diagnosis of a cerebral tumour. Before his admission, within a month, the appearance of his optic discs had changed sufficiently to confirm the suspicion of raised pressure. Case X also developed a measurable swelling of his optic discs within a few days of being first seen in the out-patient department.

Sudden Death

Quite apart from the obvious need to diagnose all operable conditions as soon as possible our responsibility is even greater as far as this condition is concerned because of the special danger of sudden death. Up to the time of publication of his Thesis, Grossiord had discovered reports of sudden death in 14 cases out of 72; at least 2 cases have since been reported (Shaver, 1940), and in the series reported here, Case III died suddenly seven days after a ventriculography without there having been

any change in her condition previously to suggest a deterioration, Cases I and XI were both the subject of sudden deterioration that did not yield to the usual surgical emergency procedures. Indeed it is plain that there is only one surgical procedure that is safe in this condition and that is a radical attack on the tumour; unilateral ventricular tapping is clearly fraught with danger, suboccipital decompression (XXII) has had equally fatal results. It is considerations such as these that should make every neurosurgeon hesitate before setting up a ventricular drain to relieve pressure in a patient the nature of whose lesion is not known for certain. It is apparent that these tumours are not as rare as was once thought and if always kept in mind as a possibility they may prove to be commoner still.

Special Investigations

C.S.F.—The findings are of no value whatsoever. For the sake of completeness they are summarized in Table III for those cases in which the C.S.F. was examined, it will be noted that in only 3 patients was the lumbar pressure normal (Cases IX, XX and XXV).

Table III.—Cerebrospinal Fluid Findings

Case	*Pressure*	*Cells*	*Protein mg. per cent*	*Lange*	*W.R.*	*N.A. and Pandy*
Case I	300+	1	55	Normal	—	
Case II	260 mm.	1	55		—	
Case III	300+	0	35		—	
Case IV	300+	0	20		—	
Case V	210 mm.	2	60		—	
Case VI	220 mm.	1	45			
Case VII ..	300+	0	25	Normal	—	—
Case VIII ..	250 mm.	1	20	Normal	—	—
Case IX	160 mm.	0	20	Normal	—	—
Case X	240 mm.	0	30	Normal	—	—
Case XIV ..	300 mm.	0	30	Normal	—	—
Case XV ..	300+	0	45	Normal	—	—
Case XIX ..	330+	0	30		—	—
Case XX ..	110 mm.	0	10		—	
Case XXI ..	220 mm.					
Case XXV ..	150 mm.	3	25			

Radiological signs.—These in all cases are the signs of raised intracranial pressure only and are of use only as a negative investigation.

Value of the electro-encephalogram (E.E.G.).—It has been stated that the E.E.G. has no value in this condition. This is not however entirely true. An abnormal E.E.G. was recorded in 10 of these cases, but the abnormality was non-specific (Cases VI, IX, XIV, XVI, XVII, XXII, XXV, XXVI, XXVII, and XXVIII); the nearest approach to a localization that could be attempted on these records was "raised intracranial pressure: a

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lesion of the deep central structures, or in the posterior fossa." In 5 other cases the E.E.G. was recorded as normal. It is the writer's contention that there is some value in a negative or non-specific record in these cases. For whereas one would expect just such a record in the presence of these benign non-destructive lesions, lateralizing features, at least can be expected in destructive lesions of the hemispheres. It should be recalled that of the cases previously quoted where localization was the problem in a case presenting with headache and papillœdema only, in each one of the tumours that proved to have a hemisphere lesion and in which a record was taken, an E.E.G. of lateralizing value was recorded. This is a minor point perhaps, but a small link in the chain of evidence that may lead one to deduce correctly by exclusion the presence of a colloid cyst.

Table IV is a tabulated record of the age of onset, sex, duration of symptoms and final result. It will be seen that 9 out of 29 died; that there are 11 females against 18 males; the age of onset varies from 21½ to 52 with the greatest age incidence between 36 to 40 (10) for the onset of the

TABLE IV

Case	*Sex*	*Age of patient at onset*	*Duration of symptoms*	*Result*
I ..	M	31 years	4 months	Died
II ..	F	38 years	7 years	Relieved by operation
III ..	F	52 years	6 months	Died following ventriculography
IV ..	M	36 years	4 months	Relieved by operation
V ..	M	42 years	3 months	Relieved by operation
VI ..	F	37 years	At least two years	Died following operation
VII ..	M	31 years	9 months	Relieved by operation
VIII ..	M	38 years	2 years	Relieved by operation
IX ..	F	40 years	5 years	Relieved by operation
X ..	M	38 years	3 years	Relieved by operation
XI ..	M	35 years	7 days	Died following ventricular tap
XII ..	M	38 years	5 months	Relieved by operation
XIII ..	M	29 years	5 years	Relieved by operation
XIV ..	M	26 years	3 months	Relieved by operation
XV ..	M	27 years	8 weeks	Relieved by operation
XVI ..	F	24 years	2 years	Relieved by operation
XVII ..	M	26 years	3 months	Relieved by operation
XVIII ..	M	34 years	1 year	Died after operation
XIX ..	F	23 years	2 years	Died after operation
XX ..	F	21½ years	4½ years	Relieved by operation
XXI ..	M	47 years	12 months	Relieved by operation
XXII ..	M	50 years	6 months	Died following operation
XXIII ..	M	39 years	3 years	Died following operation
XXIV ..	M	29 years	9 months	Relieved by operation
XXV ..	F	37 years	6 years	Relieved by operation
XXVI ..	M	40 years	3 weeks	Relieved by operation
XXVII ..	F	23 years	3 weeks	Relieved by operation
XXVIII	F	29 years	2½ years	Relieved by operation
XXIX ..	F	48 years	10 days	Died

first symptom, with 4 cases between 31 to 35 and 4 between 26 to 52. By far the greatest number had six months or less of history before entering hospital (13), 4 cases more than six months but less than twelve months, 4 cases more than twelve months and less than two years, while only 4 cases had a history of five years or more. 2 of the fatal cases had the shortest history, seven days and ten days only (Cases XI and XXIX). These figures are similar to those recorded elsewhere; in Grossiord's series there was a balance in favour of males 46 to 30 females and age of onset varied from 20 to 50.

Conclusions

After considering these cases carefully, especially after comparing them with a large series of other types of space-occupying lesions of all sorts and locations certain conclusions can reasonably be drawn. Let there be no mistake however. Dandy's conclusion that it is usually impossible to make the diagnosis with certainty prior to ventriculography remains unshaken (Dandy, 1933). Nevertheless, the writer is convinced that although there are no pathognomonic symptoms or signs of this condition, there are certain features each occurring rather more frequently in this condition than in any one other condition, while the combination would justify a diagnosis of third ventricular cyst. In this series the diagnosis was made correctly clinically in one case only (Case XV) and suggested as a possibility in the differential diagnosis of 4 (Cases IX, XVI, XVII and XXVIII). It is felt that this could be improved upon. On the other hand the diagnosis has been frequently suggested in cases that subsequently were found to have some other sort of tumour. It is considered that the reason for this is the false belief that the diagnosis should be made only when there is a strong history of paroxysmal attacks of sudden headache and when there is a dramatic postural relationship to the headache. While admitting that these features occur in cases of colloid cyst it is pointed out that they are not constant and they also occur in other tumours.

The features previously referred to are as follows: The patient would be of adult or early middle age, and complain principally of headache; the headache may be of any kind but is most likely to be frontal, equal on both sides, short lived, yet of considerable intensity when present; it may well be relieved by lying flat, and will often be accompanied by vomiting; of lateralizing symptoms there would be none but he is likely to complain of two types of seizures; he will complain either of attacks in which he abruptly loses consciousness, lies flaccid on the ground without any tonic or clonic, phases, tongue biting or incontinence of urine. These attacks may well mark the climax of a severe headache that has been building up over the previous thirty minutes, or may precede a period lasting one or two days in which he suffers from constant headache, nausea, vomiting

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and dulling of his wits. More characteristically he will complain of attacks in which he falls to the ground, perfectly conscious, but unable to stand "because his legs have suddenly become weak": these attacks may be preceded for a short time by subjective symptoms referred to the lower limbs. These second attacks will be short lived, may occur frequently and will be associated with no clouding of consciousness whatsoever. The only visual symptom of which he will complain will be brief amblyopic attacks or a progressive visual failure. There may be a history of a progressive, or fluctuating global dementia with no specific features about the dementia, or of sudden unexplained incontinence of urine or fæces.

On examination the only abnormal physical signs will be that of papillœdema and the type of visual failure that results from long-standing raised intracranial pressure with papillœdema; there may in addition be such false localizing signs as external rectus palsies or bilateral extensor plantar responses. An X-ray of the skull will reveal no shift of the pineal, and the signs of long-standing pressure only. An E.E.G. will reveal a non-specific abnormality of the sort that indicates raised pressure only with no localizing features. The C.S.F. will contain no abnormality but the lumbar pressure will be raised, and lumbar puncture is likely to upset the patient and precipitate a crisis.

Even in the absence of most of the features mentioned, if the patient's only symptom is headache of any kind and the only sign papillœdema, then the diagnosis must be seriously considered, especially if the ancillary aids to diagnosis fail to provide any lateralizing evidence. Furthermore, if such a patient presents in coma or near coma, as did Case XI, with evidence of tentorial herniation, then ventriculography should be undertaken as the emergency measure and not ventricular drainage as a preliminary. For experience has taught that the surgery of patients with tumours who arrive under the care of the neurosurgeon in coma, has under the more usual circumstances the most disappointing results because of the malignant nature of the majority of these tumours. If ventriculography as an emergency diagnostic measure merely succeeds in tipping the scales against these patients a little more, less harm is done than when a patient with a benign, operable tumour of the third ventricle has the scales hopelessly weighed against him by unilateral ventricular drainage which affords no relief but merely so alters the pressure relationship inside the skull, with a collapsed, draining ventricle on one side and a ventricle grossly dilated under pressure on the other, that irreparable damage is the result.

Summary

Twenty-nine cases of colloid cyst of the third ventricle of the brain are reported in detail. While 9 cases presented with anomalous features

suggesting a false localization of the tumour, the rest had neither strongly localizing features in the history nor localizing signs in the examination. These latter presented either as a problem of localization in cases presenting with headache and papilloedema only, or with a progressive dementia, or with a strongly fluctuating episodic history.

A comparison is made with the clinical features and the results of special investigations in cases with tumours in other situations but with similar features that presented in the National Hospital, Queen Square, between the middle of June 1947 and December 31, 1949, a series comprising 361 consecutive tumours of all types and from which these other tumour cases were selected.

Frequently recurring symptoms, such as the type of headache, attacks of loss of consciousness and attacks of sudden pareses of the lower limbs are analysed. The value of special investigations in these tumours is discussed.

The conclusion is arrived at that, although it is not possible to make this diagnosis with certainty without the aid of air replacement studies, there is a combination of clinical features which should suggest the presence of such a tumour.

ACKNOWLEDGMENTS

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CORTICOFUGAL CONNEXIONS OF POSTERIOR ORBITAL SURFACE IN RHESUS MONKEY

BY

PATRICK D. WALL[1,3], PAUL GLEES[2], AND JOHN F. FULTON[1]

THIS report deals with a projection system originating in that part of the orbital surface of the frontal lobes of monkeys which has been designated area 13 by Walker (1940) and which corresponds roughly to area FF of von Bonin and Bailey (1947). As first shown by Spencer (1894), stimulation of this neocortical area causes conspicuous changes of blood pressure and arrest of respiration; its bilateral ablation is followed by marked motor hyperactivity (Ruch and Shenkin, 1943; Livingston *et al.*, 1948), i.e. incessant restlessness and pacing.

Thalamic interconnexions of the orbital surface have not yet been clearly traced. Thus Walker (1940) remarks, "This area presumably receives a projection from the medial part of the medial thalamic nucleus." Von Bonin and Green (1949) state that the thalamocortical connexions of the area are less than might be expected. They conclude that the medioventral part of the medial thalamic nucleus projects to the orbital surface, although none of their lesions is restricted to the neocortical region with which this paper is concerned. No specific Marchi studies have yet been reported on the corticothalamic relationship of the posterior orbital surface.

In 1948 the existence of projections from this area to the hypothalamus in man were reported personally by M. Meyer to Le Gros Clark of Oxford; the fibres were shown by a silver technique in a single case of human frontal lobotomy. Von Bonin and Green (1949) found signs of retrograde degeneration after a lesion which involved both the area which is to be studied here and a small amount of allocortex which runs along the posterior edge of area FF. Ward and McCulloch (1947), using strychnine applied to the orbital surface, recorded spikes from the nucleus paraventricularis and the posterior hypothalamic area.

We here offer evidence of a direct fine-fibred projection from the posterior orbital surface to the hypothalamus and caudate nucleus.

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Methods

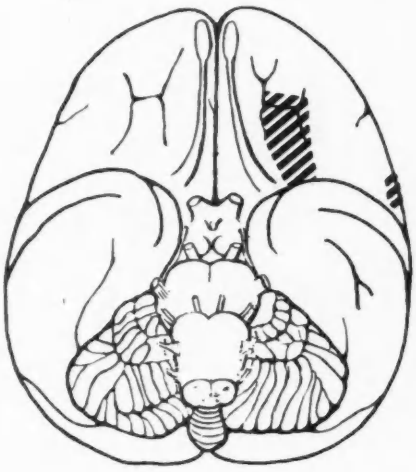
Three rhesus monkeys (*Macaca mulatta*) were operated on under amytal anæsthesia. A bone flap was turned to expose the left cerebral hemisphere and the orbital surface was brought into view by gentle retraction of the lateral border of the frontal pole. In one case the area to be undercut was first identified by stimulation, thus defining the limits of the region from which respiratory and blood pressure changes could be obtained. The cortex was undercut with a thin spatula. In animals M1 and 2 small accidental lesions of the lateral surface occurred but in M3 the lesion was clean and isolated. The dura was closed, the bone flap replaced, and the muscle and scalp closed in layers.

Recovery was uneventful although all animals showed mild hyperactivity. After ten days the animals were sacrificed. The area of the lesion was studied by the Marchi method to determine the extent of the lesion. The areas to which it was thought fibres might project were studied by the fine-fibre silver method of Bielschowsky as modified by Glees (1946) and Wall (1950).

Results

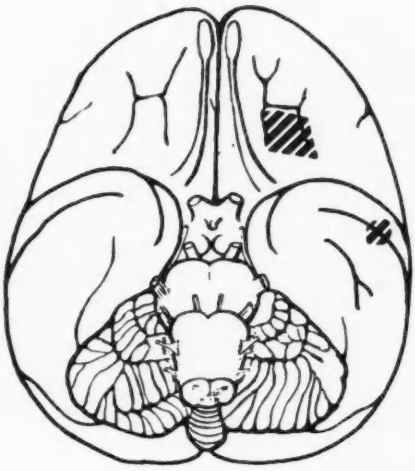
The extent of the lesions in the three monkeys is shown in figs. 1, 2 and 3, and the depth of the lesion in fig. 4. In view of the difficulties involved in the fine-fibre staining technique, we have recognized degeneration as occurring only in the following circumstances: first, when there was clear contrast between the operated and control sides stained simultaneously; second, when the section showed a clear agranular background with discrete parallel-sided fibres; third, only gross distortions of fibre shape and termination were accepted as evidence of degeneration.

Caudate nucleus.—Clear degeneration occurred in the head of the



M 1

Fig. 1.



M 2

Fig. 2.

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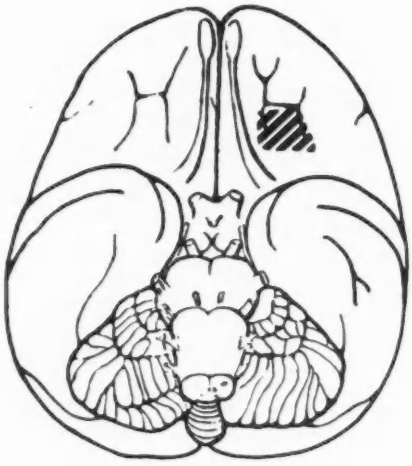

FIG. 3.

FIGS. 1, 2, 3.—Extent of the lesions produced in M1, 2, 3 shown by cross-hatched areas.

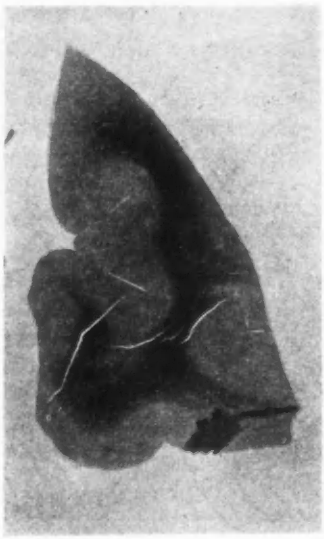

FIG. 4.—Depth of the lesion on the orbital surface. The lesion is stained in black by osmic acid and is shown involving only cortical structures. The sulcus principalis on the left and the caudate nucleus above the lesion are shown not to be affected.

caudate nucleus. The degeneration was present in relatively high concentration, especially in the upper part of the caudate head. This degeneration was clear in both animals M1 and 2.

Putamen.—No significant degeneration.

Globus pallidus.—No significant degeneration.

Thalamus.—Careful search of the thalamic nuclei and their immediate surroundings revealed no obvious degeneration. The dorsomedial nucleus did not contain degenerating endings nor were there any in the reticular formation.

Hypothalamus.—In M1 and 3 there were striking signs of degeneration. It is extremely difficult to follow any fibre tract by this method but there was the appearance of fibres arriving dorsally over the optic chiasm and turning ventrally where there was evidence of fibres ending in the paraventricular nuclei and the ventromedial nucleus of the hypothalamus in its posterior part (*see* figs. 5 and 6).

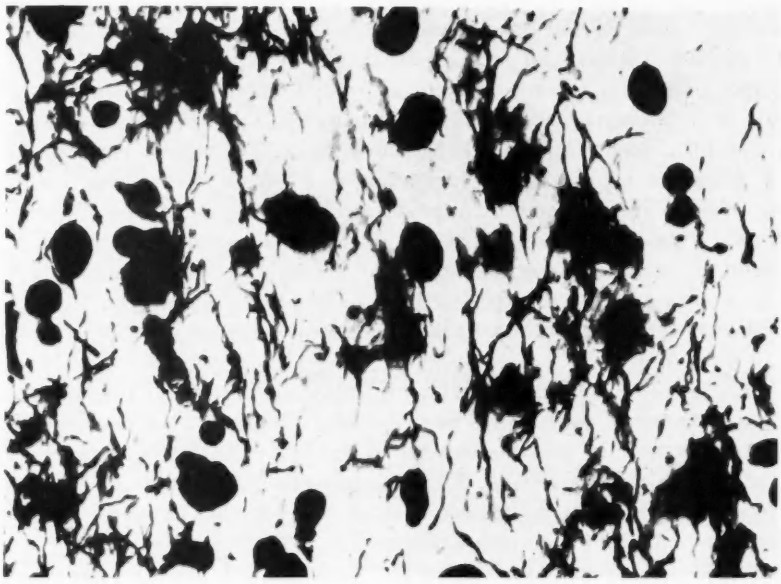

FIG. 5.—Fine fibres degenerating within the hypothalamus after a lesion of the orbital surface. The fine fibres are stained with silver.

DISCUSSION

Certain aspects of this study must be interpreted with care. The extent of the lesion in all directions should be considered. On its

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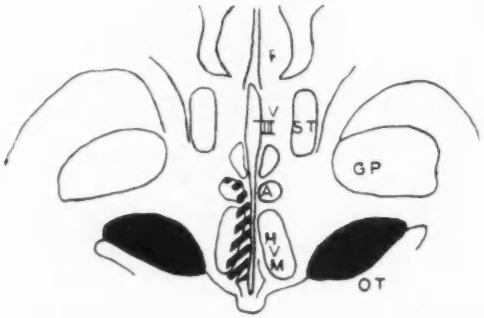

FIG. 6.—Content of the area within the hypothalamus in which degeneration was found. A, anterior hypothalamic nucleus; F, formix; G.P., globus pallidus; H.V.M., ventromedial nucleus; O.T., optic tract; S.T., stria terminalis; V III, third ventricle.

posterior border the lesion in M1 involved some of the allocortex posterior to area 13 (area FF) but hypothalamic and caudate degeneration was also seen in M2 which did not have any of this allocortex involved. The superior border of the lesions comes very close to two structures—first, the caudate nucleus, and second, the depths of sulcus principalis. The danger that fibres leaving the ventral part of the caudate nucleus may have been damaged cannot be denied although it is improbable that many would have been involved. Direct involvement of the caudate in the lesion cannot explain the degeneration seen within the caudate since the areas of degeneration were more superior and posterior at some distance from the orbital surface. However, to settle this question finally, we intend to carry out thermocoagulation lesions of the cortex to avoid any possible damage to deep structures. There is no doubt from sections of the area of the lesion (fig. 4) that the depths of sulcus principalis were not affected.

The accidental lesions in M1 and 2 were not important because the same picture was seen in M3 in which there was no extraneous injury of the cortex. The possible damage to the lateral border of the frontal lobe caused by retraction of the edge to expose the orbital surface has probably little significance since Marchi degeneration was not seen in this area.

It is not yet possible to estimate the density of fibre degeneration since homogeneous staining over large areas of the central nervous system is difficult to obtain with this technique. Similarly, we cannot claim that this study has shown all the projections of the orbital surface. The functional significance of the two pathways has been investigated by one of us (P. D. W.). It is clear that the pathways mediating the blood pressure effects resulting from orbital surface stimulation run quite

separately from those responsible for the respiratory reactions. This has been shown by making discrete lesions in the hypothalamic area (thus cutting the orbital projections); this abolishes the blood pressure response to further orbital surface stimulation but leaves the respiratory control unaffected. Caudate stimulation in the area in which the fibres from the orbital surface are believed to end cause only respiratory changes with minimal effect on the systolic pressure. The question remains as to what pathways are concerned in the hyperactivity which follows upon ablation of the orbital gyri. Such hyperactivity appears to be inhibited by discrete hypothalamic lesions, but a further analysis of this point is needed.

SUMMARY

Lesions were made in the posterior orbital surface of three monkeys (*Macaca mulatta*). The animals were sacrified ten days after the operation and fine-fibre degeneration was investigated by a silver staining method. Direct projections were shown from the orbital surface to the ventromedial and the paraventricular nuclei of the hypothalamus and to the caudate nucleus (fig. 7). Physiological work on the significance of these projections is discussed.

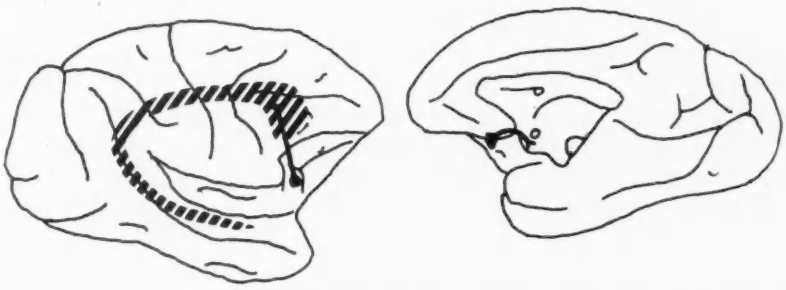

FIG. 7.—The two directions in which fibres have been shown to project from the orbital surface. On the left the caudate nucleus is shown cross-hatched, receiving a projection into the head of the caudate. On the right the projection to the hypothalamus is shown.

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NERVOUS AND MENTAL DISORDERS IN CUSHING'S SYNDROME

BY

JOHN D. SPILLANE

THE physical and metabolic changes that characterize Cushing's syndrome are well known. Whether the disorder is associated with pituitary, adrenal or, rarely, thymic or ovarian dysfunction, striking physical and biological alterations result which in many instances enable diagnosis to be made. Probably in all cases there is hyperactivity of the cortex of the adrenals, and hyalinization of the basophil cells of the pituitary is usually found at autopsy. When the disease appears in the young male or female recognition is often easy. But in later life, especially in women at the climacteric, the clinical picture may be confusing. Many mild and apparently incomplete forms are met with. On the other hand, at autopsy, the diagnosis is sometimes shown to have been wrong, or no endocrine lesion is found.

Experience with proved cases of the disorder shows that truncal obesity, plethora, plum-coloured facies, hypertension, polycythæmia and purple striæ distensæ are commonly present. In the male there is often some loss of libido while hair growth may be retarded or, rarely, excessive. Amenorrhœa and hirsutism are the rule in the female. Glycosuria, reduced sugar tolerance, increased urinary excretion of 17-ketosteroids and sometimes polyuria and polydipsia are other signs. Osteoporosis is common.

The syndrome is said to occur twice as often in females as in males and it is usually encountered in the third and fourth decades. Adrenal cortical basophilism is rare in adult males; it is usually met with in adult females. Libido and sexual development may be increased or precocious in the adrenal type of the disorder; in the pituitary type they are frequently retarded. In children epiphyseal union is retarded in pituitary basophilism and may be precocious in adrenal basophilism. True virilism seems only to occur with hyperplasia or tumour of the adrenal cortex and with arrhenoblastoma. The latter rarely produces the circulatory and metabolic disorder which characterize pituitary and adrenal basophilism.

It is not always possible to differentiate between pituitary and adrenal basophilism. The clinical features may be identical—whether there is glandular adenoma or hyperplasia. In pituitary basophilism the sella turcica is rarely enlarged and the well-known pressure effects of pituitary enlargement do not usually occur. An adrenal cortical tumour is often not palpable—unlike an ovarian tumour. A thymic neoplasm can be often demonstrated radiologically. Perinephric insufflation of air may outline an adrenal tumour in an X-ray photograph but a normal appearance does not exclude it and exploration may be necessary. A group of androgenic hormones called 17-ketosteroids is markedly increased in patients with adrenal cortical tumours and is normal or only moderately increased in patients without

these tumours (Crooke and Callow, 1939). In pituitary basophilism the urinary excretion of 17-ketosteroids is rarely more than three times the average daily amount for the normal of the same age and sex. In adrenal cortical basophilism the excretion is rarely less than four times the average daily amount (Crooke, 1948).

The development of the disease is usually insidious and an increase in weight is commonly the first sign. The obesity is confined to the trunk, especially affecting the lower abdominal wall. The face broadens and takes on a plum-colour. The neck thickens and there is often a diffuse upper dorsal kyphosis. The general appearance of the patient alters considerably. There is much variation in the rapidity with which these changes come about. In some the whole course of the disease is rapid and a fatal outcome may result in a few months. Usually, however, the course is longer, and natural remissions and exacerbations occur. The disease is commonly said to be fatal within five years but one of Cushing's original cases survived twenty years. Waxing and waning of the symptoms and signs have several times been noted by the writer.

The administration of hormones, deep X-ray therapy and radon seed implantation of the pituitary gland have been advocated and carried out. Hormone therapy has not so far proved useful. Although striking improvement may follow the second and third methods of treatment, the overall results are disappointing. Temporary improvement may occur but relapse follows. Deep X-ray therapy is not without risks (*see* Case I).

A B C

FIGS. 1A, 1B and 1C (*Case* 1).—Showing the progressive facial change during the course of the disease.

Case I.—G. K., male, aged 26. This young man was called up for military service in February, 1942, at the age of 18 years (fig. 1A). His weight was then 140 lb., height 5 ft. 4 in., pulse 70 and blood pressure 120/84. In October 1942, he was operated upon for appendicitis. There is no record of the operative findings but a few days

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afterwards he developed further abdominal pain with vomiting and on reopening the abdominal cavity it was found that there had been an intraperitonial hæmorrhage. The cause of the bleeding was not ascertained. His blood pressure was then 180/120. He complained of headaches; his weight was then 165 lb. Blood pressure remained in the region of 180/120, apex beat was forcible and there was no evidence of retinal arteriosclerosis. Blood count: R.B.C. 5,100,000, W.B.C. 4,260, Hb 100 per cent. Urine contained a trace of albumen, blood urea was 19 mgm. and with normal urea concentration test. Visual fields were normal and there was no enlargement of the pituitary fossa on X-ray examination. While under investigation it was observed that his face became increasingly florid (fig. 1B).

He remained in hospital until June 1943, by which time his blood pressure had risen to 240/150. There was some dyspnœa on exertion and his headaches were increasingly disabling. No renal cause for his hypertension was discovered. Cystoscopy, pyelography and repeated urea clearance tests were normal.

In November 1943, his appearance became more striking (fig. 1c). His face was red, his neck bull-shaped, and his body was very fat. He weighed 180 lb. His limbs remained spare and were mottled and cyanotic. On the lower abdominal wall on the left side there developed three angry, purple coloured splits. They were tender. Other bluish-red striæ appeared about the axillæ and on the inner surfaces of the upper arms. The hair on his face was scanty; he shaved only every other day. The pubic hair was ample and of male distribution. He was now round-shouldered. His blood pressure was then 220/140 and the heart was slightly enlarged to the left. Blood urea was 28 mgm. per cent.

A diagnosis of Cushing's syndrome was made and he was transferred to another hospital for irradiation of the pituitary gland. It was there noted that dystrophic changes were occurring in the nails of his feet and hands. There was a superficial hæmorrhage in the right retina; no papilloedema. A dose of 6,000 r was given to the pituitary region over a period of thirty-two days—in November, December 1943. There was no appreciable reaction and he was discharged from hospital on 4.1.44. He lost his plethoric appearance, his headaches subsided and the purple striæ on abdomen and arms gradually faded. On discharge form the Army on 12.3.44 his blood pressure was 180/120. His weight was 160 lb.

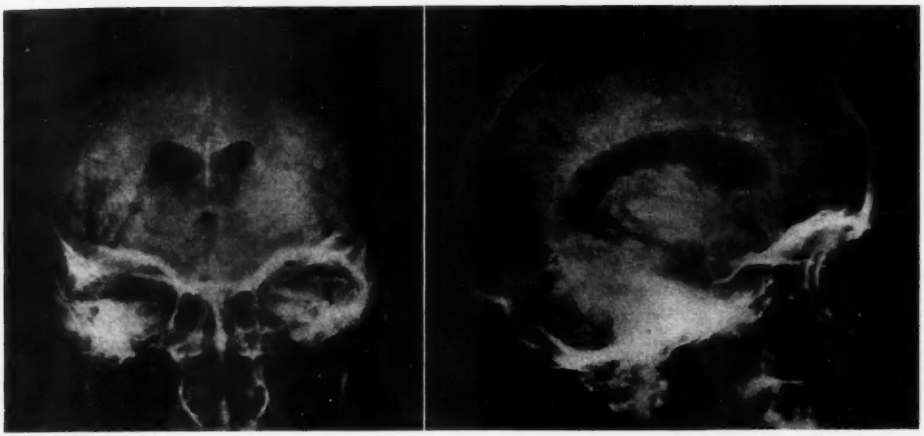
His general condition continued to improve and there was a striking return to his normal appearance and activities. He remained very well and at work, without symptoms, during the following year. During 1946 he complained of tiredness and visual weakness. He consulted his doctor in August 1947, and complained of being forgetful, of lacking energy, and of failing vision. At first his manner was unchanged but after some months at home his parents thought he was deteriorating. He slept for long periods during the day. He went out rarely and ate little. At other times he was thirsty and drank large amounts of water. In January 1948, he was admitted to hospital under my care.

He complained of forgetfulness, fatigue, occasional diplopia, failing of vision and hesitation in speech. He was rather pale, weight 143 lb., blood pressure was 125/80. His speech was slurred and his memory grossly inadequate. He could not remember the main events of his illness, where he had been treated, what year he was abroad. He was lethargic, said little spontaneously, and was content to remain in his bed—dozing, or smoking a cigarette. Both temples bore the marks of superficial X-ray burns. The pupils were dilated and unequal and there was early bilateral optic atrophy, but no swelling of either optic disc. Vision was 6/36 in the right eye and 6/18 in the left. Both visual fields were contracted peripherally. There were no scotomata. Other cranial nerves were normal. Power in all limbs was fair; deep reflexes were exaggerated but the plantar reflexes were normal. The left abdominal reflexes were absent. There was no sensory alteration. Urinary 17-ketosteroid excretion was normal (17 mgm. per twenty-four hours).

Lumbar puncture revealed a clear cerebrospinal fluid under normal pressure

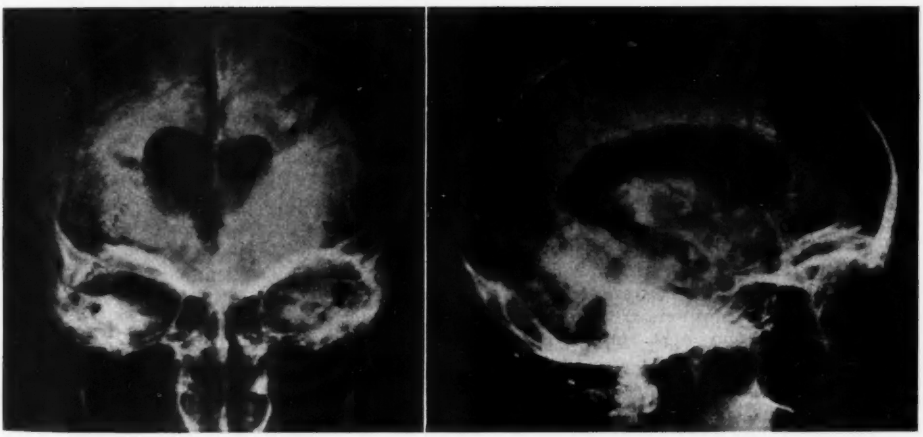
(110 mm.); protein content 60 mgm. per cent; Wassermann negative in blood and fluid. X-ray of skull and chest showed no abnormality. Lumbar air encephalography was performed on 25.1.48 and 100 c.c. of air were introduced. X-ray examination revealed that there was early cortical atrophy, and asymmetrical dilatation of the lateral ventricles with excess air over the frontal and parietal lobes (figs. 2A and 2B). Sugar tolerance tests were normal.

There was no remaning polycythæmia (R.B.C. 4,900,000 and Hb 100 per cent) and only faint pinkish striæ were visible about the lower abdomen and flanks and



A B

FIGS. 2A and 2B (*Case* 1).—Air encephalogram showing the progressive cerebral atrophy that developed (with blindness) after pituitary irradiation.



A B

FIGS. 3A and 3B (*Case* 1).—Air encephalogram one year later (i.e. five years after pituitary irradiation).

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upper parts of his thighs. It was concluded that a cure of pituitary basophilism had been achieved, but that irradiation necrosis of the brain and visual tract had set in. He was discharged from hospital on 30.1.48.

He has been followed since that time and progressive dementia and visual failure have been recorded. Encephalography was repeated on 15.4.48 and 9.3.49 (figs. 3A and 3B). There is now complete blindness due to primary optic atrophy and he is incontinent and bedridden. Encephalography revealed progressive cortical atrophy. There has been no significant osteoporosis.

Case 2.—M. C., male, aged 26. He was admitted to hospital on 16.9.48, complaining of headaches, insomnia, bouts of depression and periodic indigestion. He had served four years in the Army and his first illness of note occurred in 1943. At that time he had frequent boils and septic skin lesions. In 1945 he had a temporary anxiety state. In 1946 he began to complain of pains in his back and limbs. He was admitted to a military hospital and treated for "subacute rheumatism." His blood count was normal (R.B.C. 4,880,000, Hb 93 per cent). While in hospital he complained of minor fears, battle dreams, and insomnia. He was seen by a psychiatrist who recorded mild ideas of persecution and feelings of friendlessness. He was invalided to the United Kingdom and while in a military hospital proved unruly and truculent. He thought he had been "given the truth drug against his will," and that he was being unfairly treated and that people were "against him." He was given continuous narcosis and, later, electrical convulsant therapy and improved somewhat. He appeared to have no memory of his former difficult behaviour and expressed exasperation at having been detained in a mental hospital to which he had been transferred for treatment. On invaliding from the Army in January 1947, there were no remaining psychotic symptoms. His blood count was then—R.B.C. 5,440,000, Hb 90 per cent.

On return home his mother noticed a profound change had taken place in his physical appearance and character. Formerly he was of normal weight (142 lb.), height 5 ft. 2 in., and healthy in appearance (fig. 4A). He had been well-behaved, popular, and energetic. Now he was obese (178 lb.), red-faced, bull-necked, and coarse in manner and speech. He could not sleep at night, idled about during the day and professed dislike of most forms of work. When, in November 1947, his outbursts of temper, surly behaviour and lethargy became intolerable, his mother persuaded him to enter a county mental hospital for treatment. On admission it was recorded that he was listless and indifferent and experienced auditory hallucinations. He received electrical convulsant therapy and improved. He was discharged in January 1948.

During 1948 he did occasional light jobs but he was dissatisfied and quarrelsome, and generally proved a difficult person to manage. He was brought to hospital in November 1948, because of his obesity and odd behaviour.

He was a short pugnacious-looking individual, surly, red-faced and obese (fig. 4B). He weighed 180 lb. His face was coarse-skinned and blotchy; he had a thick neck, round shoulders and pads of fat about the neck and scapulæ. His abdomen was protuberant and his limbs thick proximally. Hands and feet were small and not thickened. Nails were normal. The thighs were tense and cyanosed with vivid purple streaks running across the buttocks, groins and flanks. Less gross markings were seen on the inner aspects of the arms, below the axillæ. Penis and scrotum were small but the pubic hair was normal in character and distribution.

Blood pressure was 180/130, there was no cardiac enlargement. There was no alteration of power, tone or reflex function and sensation was unimpaired. Cranial nerves were normal. Vision 6/6 R. and L. Fundi normal. Fields normal. There was no tenderness or mass in the abdomen.

Blood count: R.B.C. 6,200,000; Hb 124 per cent; C.I. 1·0; W.B.C. 8,000 with a normal differential count. Urine: acid, no albumen or sugar; no casts, culture

A

B

FIGS. 4A and 4B (*Case* 2).—Appearance before and during illness.

sterile after twenty-four hours. Urea concentration tests normal. Normal intravenous pyelogram. Fasting blood sugar 110 mg. with a normal glucose tolerance curve.

X-ray examination of skull and skeleton revealed no abnormality.

Blood Wassermann negative. Cerebrospinal fluid pressure 110 mm. (lumbar), with a normal fluid; protein 30 mgm. per cent, cells 2, negative W.R. and normal Lange curve.

Urinary excretion of 17-ketosteroids—30 mg. per twenty-four hours.

He left hospital abruptly after X-ray therapy to the pituitary gland had been proceeding for four days. He had received 1,700 r.

During the following year his weight remained more or less stationary and his physical appearance remained gross and coarse. Blood pressure was usually in the neighbourhood of 180/120 and his red cell count near 6,000,000; Hb 120 per cent to 125 per cent. Purple striæ came and went; some remained raw and purple-looking for many weeks, others would appear rapidly, deepen in colour and fade spontaneously. But these streaks never became colourless and nearly always remained a pink or lilac colour. Insomnia remained an obstinate complaint. He experienced burning sensations of heat about the head and neck. He talked freely about the harm that had been done to him and of the injustice that had been meted out to him. He disliked most company and led a solitary, anti-social, idle existence.

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When last seen in November 1949, his physical condition was unchanged but his mental state had deteriorated.

Case 3.—B. L., male, aged 24 years. He was admitted to hospital in September 1948. He complained of the appearance of "marks of blood vessels appearing on his body—on the lower abdomen, thighs and upper arms." They had first appeared on his arms in 1944 when he was serving in the Army. They came and went over a period of one year and then finally faded altogether. But they had reappeared during August 1948, and then also affected the lower part of his trunk and the thighs.

He had enjoyed good health until 1944. He volunteered for military service in 1943. He was then aged 18 years, 5 ft. 11 in. in height, weighing 156 lb. Shortly afterwards he first noticed that marks were appearing on his arms. He said they were at first reddish linear streaks, one or two inches in length, and one-quarter to one-half inch in width. They developed on the inner and upper aspects of both arms—simultaneously. In a few weeks they deepened in colour and one or two of them were sore to touch. Ultimately, the majority (there were five or six on each arm) became a livid purple and caused him some alarm. He consulted his medical officer, but apparently a diagnosis was not made. The streaks faded—sometimes rapidly and sometimes very slowly—and others developed concurrently in very adjacent sites. He thinks that twenty or more developed on both arms over the period of a year.

In October 1944, he grew irritable and preoccupied with himself. One day when writing a letter home he broke down and cried. He felt something was radically wrong. He saw his medical officer and was reassured. A few days later he was involved in some emotional upset in his bivouac. His fellows thought he was "rather off his head." They liked him and felt he was not well. He complained of increasing fatigue, inability to attend to his duties, irritability and loss of appetite. On admission to sick quarters he cried bitterly, expressed ideas of shame and talked of suicide. On the following day he said both his arms were paralysed. He could not lift them above his head. He was transferred to a psychiatric department of a general hospital in France where he seems to have remained for the next four months. He was regarded as suffering from a psychoneurosis with hysterical manifestations.

He was ultimately invalided to the United Kingdom. The weakness of his arms was thought to be hysterical, but the periodic purple streaks on his arms —and at this time also across the anterior axillary folds—were taken to indicate venous congestion as the result of some costoclavicular pressure. X-ray examination disclosed no cervical ribs and his radial pulses were not affected by any cervical or shoulder manœuvre. He was placed in category B1 and returned to duty. He was taking many aspirin tablets daily for the aching in his arms and for his sleeplessness. During the year 1944 he had put on about twenty pounds in weight.

Then, one day in August, 1944, he noticed a blurring of vision and complained of some pain in the left eyeball and described a scotomatous defect on a page of print when he attempted to read. Seen by an ophthalmologist about one week after its onset it was recorded that V.A.R. was 6/6 and V.A.L. 6/60. Examination of his visual fields confirmed that there was a scotoma, central in position, measuring 3° in radius. The upper level of the scotomatous defect was flat; there was some swelling of the retina of the affected eye just above the macula. He was admitted to hospital but no further abnormality was found. Vision began to improve after one month from the time of onset of this episode and he was ultimately discharged from hospital with a diagnosis of retrobulbar neuritis.

He states that his vision remained much the same in the affected eye. On release from Service he weighed 175 lb. and the central scotoma was still present with vision in the affected eye 6/60.

For the next year he remained active and well but his weight increased to

190 lb. He was married early in 1948. He experienced no sexual difficulties. He did not worry excessively but was sometimes troubled by sleeplessness.

In September, 1948, streaks on his upper arms reappeared. Within a fortnight a few of them had become red and angry-looking. He recognized them as similar to those he had had when in the Army four years previously. But this time they were also appearing on his thighs. He was referred to me in September, 1948, and was admitted to hospital for investigation.

He was then 5 ft. 11¾ in. in height, and weighed 190 lb. His face was not particularly flushed or obese. There was a poor growth of hair on the chin: he shaved every other day. Pubic hair was normal. His obesity was mainly confined to the trunk and abdomen; he thought his thighs and buttocks had enlarged. Characteristic purple striæ were seen about the inner aspects of both upper arms and about the lower abdomen, buttocks and thighs. When first seen few of them were as purple as they later appeared. The faded markings of the streaks that had troubled him while in the Army were visible. External genitals were normal. Blood pressure 150/90. Heart not enlarged and retinal arteries healthy. Examination of the nervous system revealed no defect other than a central scotoma (3° radius) in the left field of vision. There was no significant pallor of the optic discs. Respiratory system was normal. There was no mass or tenderness on palpation of the abdomen. Urine normal. Blood count: R.B.C. 6,200,000, W.B.C. 7,000, with normal differential count. Hb 121 per cent. Fasting blood sugar 101 mg. per cent. with a low-normal sugar tolerance curve. Wassermann reaction negative in blood and cerebrospinal fluid. The cerebrospinal fluid was normal. X-ray of skull was normal and there was no indication of osteoporosis of the skeleton. Urinary excretion of 17-ketosteroids (of the urine) was 26 mg. per twenty-four hours.

He remained in hospital for one month and during this time he felt well but was worried about the reappearance of the striæ. He associated them closely with the period of nervous disturbance he had experienced while serving in the Army. He was now married and had a good post and there were no emotional problems. The diagnosis was explained to him but radio-therapy to the pituitary gland or exploration of his adrenal were not advised. He was willing to be kept under close observation and proved very co-operative.

He was seen every few weeks for the following year. His weight increased to 205 lb. but his general health was good. He worked well and did not complain of fatigue, insomnia or headache. At times he complained of backache but repeated X-ray studies of the spine showed no sign of collapsing vertebræ or other evidence of osteoporosis. His blood pressure remained in the neighbourhood of 150/90, 160/90. Blood counts remained at a six million level for five months and then dropped to a level of about 5½ millions. His hæmoglobin remained at 121 per cent to 124 per cent levels for a similar period and is now 110 per cent. Blood sugar was always about 100 mgm. per cent and at no time has glycosuria been recorded. Blood sugar curves were repeated on two occasions and there was no significant abnormality.

Meanwhile, his striæ became more noticeable. Those about the axillæ and upper arms never developed the intense hue of those on the lower part of his body, but they persisted for approximately nine months. On the abdomen and about the groins the streaks became broad and livid. Some faded as others appeared—but the grosser markings have not yet shown any sign of fading. Sometimes his thighs were cyanosed and blotchy and he had frequent acneform eruptions.

Throughout this period of observation his personality has remained unchanged.

Case 4.—P. S., male, aged 21. This young man was referred to me from an orthopædic department in March, 1949. In December, 1946, while serving in

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the Army in Italy he was involved in a road accident and sustained a fracture of the right radius and ulna. He was now complaining of backache.

He was an intelligent young man, cheerful, co-operative and not in the least inclined to exaggerate. He was obese and high-coloured. He weighed 192 lb. He was hirsute and his obesity was mainly confined to the trunk. His genitalia were small. There was normal testicular sensation. Breasts were over-developed; they were not tender. The pubic hair was of male distribution.

His thighs were purplish in colour—mottled and rather rough-skinned. In both flanks and about the buttocks were several purple striæ. He had noticed them during the past few months. There were none on the upper limbs.

There was no deformity of the spine. Forward flexion was limited by about 50 per cent owing to pain in the right hip region. Lateral flexion and rotation were fully executed. There was no muscle spasm or tenderness. There was some discomfort produced by pressure over the right sciatic nerve in the buttock; power of both lower limbs was good and there were no reflex or sensory alterations. X-ray of the lumbar spine showed no clear evidence of old fracture. There was, however, some loss of joint space between the third and fourth lumbar vertebræ and between the fifth lumbar vertebra and the sacrum. Sacroiliac and hip-joints were normal. Lumbar puncture revealed a normal fluid under normal pressure. Queckenstedt test was normal. He was immobilized in a plaster jacket and his pain was relieved.

Meanwhile, investigations were pursued in relation to his obesity and the appearance of the purple striæ. He said that he had put on 22 lb. in weight in the past two years. The marks on his lower abdomen and groins had not caused any discomfort. They had been coming and going for approximately six months. The more obvious streaks had not faded much but he thought their colour varied from time to time. He had suffered no headache or insomnia and had remained his normal cheerful disposition. A sister said that during the past two years he had "grown terribly fat—but he was just the same person." He was energetic and enjoyed his work as a student.

Blood count: R.B.C. 6,030,000, hæmoglobin 122 per cent, W.B.C. 5,200 per c.mm. Blood pressure was initially 170/100 and much the same readings were obtained daily during his stay in hospital. There was no cardiac enlargement and peripheral and retinal arteries were normal. There was no glycosuria and glucose tolerance was normal. X-ray of skull and ribs and spine disclosed no abnormality other than that noted above. The pituitary fossa was normal. Intravenous pyelography was normal and no tenderness or mass about the loins was ever noted. The excretion in the urine of 17-ketosteroids was estimated and found to be 23 mgm. per twenty-four hours.

He left hospital in his plaster jacket and returned six weeks later. His jacket was removed and he reported that his lumbar pains were better. There were no new neurological signs. He still felt well physically and mentally and had not increased in weight or appearance. His blood count was relatively unchanged and his blood pressure remained about the level formerly noted (170/100). There was no evidence of lumbar osteoporosis. The purple striæ were more marked, especially about the buttocks. His thighs were still discoloured and mottled.

It was decided to keep him under observation and when last seen in October, 1949, his condition had not deteriorated and radiotherapy was withheld.

Case 5.—J. T., male, aged 23 years. He served in the Army from the age of 17 to 20. On enlistment in 1944 he weighed 10 st. 4 lb., height 5 ft. 8 in., and had hitherto enjoyed good health. He noticed that during 1945, while serving in this country, he was getting stouter. In 1946, in India, he developed considerably in girth and by mid-summer he was weighing 12 st. He began to feel tired and to have headaches. In the autumn he reported sick at his unit because of his changing appearance. He was alarmed by the rapidly increasing obesity and

especially by the florid colouring of his face and neck. He had great difficulty in getting to sleep at night and during the day "thumping" headaches came on suddenly and forced him to retire to his bunk for several hours at a time. His face, head and neck flushed violently during some of these paroxysms and his whole head felt hot and burning. At times he felt giddy and unsteady; he had to be cautious about any sudden change of posture. Occasionally there was a ringing noise in his ears.

While resting in sick quarters he first noticed the purple striæ about his flanks and lower abdomen. They rapidly developed about October 1946 and formed livid, ugly streaks across the thighs and buttocks. A few appeared on his upper arms, on the inner side. At this time he had no appetite—but his weight continued to increase rapidly. He complained of backache, aching pains in the thighs, and considerable malaise and depression.

At that time his blood pressure was 160/100. R.B.C. 4,900,000; Hb 100 per cent. Fasting blood sugar was 100 mg. per cent. Glucose tolerance curve as follows:

100	120	120	140	100	mg. blood sugar
0	30	60	90	120	minutes

An intravenous pyelogram was normal. The cerebrospinal fluid pressure 200 mm. with protein content of 35 mgm. per cent. There was slight left ventricular enlargement on radioscopy.

He was invalided home in January 1947 and discharged from the Service in July 1947. His condition remained the same for the next few months. There was no polycythæmia at that time and the glucose tolerance test repeatedly showed some reduction. Daily excretion of androgens was estimated to be 11·6 mg. Daily urinary excretion of 17-ketosteroids was 22 mgm. There was some osteoporosis of the skull and of the lumbar vertebræ. He was not willing to stay further in hospital for deep X-ray therapy to the pituitary gland and he returned home. He remained there under the care of his own doctor during the winter of 1947-48, and in the autumn of 1948 he began a course of studies at a technical college. He received no treatment during this time except headache pills and occasional sleeping tablets. On discharge from the Army he weighed 13 st. His parents were concerned at his changed appearance. His face was deep red in colour and the eyes bloodshot. His neck was fat and livid and he was round-shouldered. He moved slowly, spoke little, and seemed to have lost all interest in life. He contemplated suicide. However, during the spring months of 1948 he began to lose weight. His facial appearance remained unchanged—but he felt less tired and depressed and the pains in his head and back and thighs improved. This change occurred very slowly, but by the summer of 1948 he felt sufficiently well to undertake a course of studies as a draughtsman. The striæ, during this period, were numerous and gross. Many were bright red, or pink, others were purple or brownish-red. His thighs were always mottled and the skin over them rough and pimply. He had several boils about the neck and face. By the autumn of 1948 he weighed just over 12 st.

He began his studies at this time, lived in lodgings in the city, and got on fairly well, though with considerable difficulty at first. His memory and concentration were poor, and he felt tired each morning. Nevertheless, he passed his term examination, and it was early in 1949 that he came under the writer's observation. His own doctor thought he had made considerable natural improvement during the preceding year.

He now weighed 12 st. His face was red and round. The obesity was confined to trunk and face; his limbs were slender. He was rather slow in speech and manner and volunteered little information about himself. He was easily roused to impatience or anger. He had to be dealt with tactfully and

sympathetically. Characteristic striæ were present about his lower abdomen and buttocks and thighs. There were a few on the upper limbs. His pulse-rate was 85 per min.; blood pressure 170/110. There was slight left ventricular enlargement. The retinal arteries were thin and sclerotic looking. R.B.C. 7,000,000; Hb 125 per cent; W.B.C. 10,800 per c.mm., with a normal differential count. Urine normal. Fasting blood sugar was 94 mgm. per 100 c.c. and a glucose tolerance curve revealed moderate elevation above the normal. X-ray examination of the skull and vertebræ showed osteoporosis; the pituitary fossa was normal. There was no evidence of adrenal tumour; intravenous pyelography was normal. There were nodular enlargements[1] of the costo-chondral junctions of the lower ribs (fig. 5).

Deep X-ray therapy was considered but in view of the definite improvement in his condition over the past year it was decided to keep him under observation. He

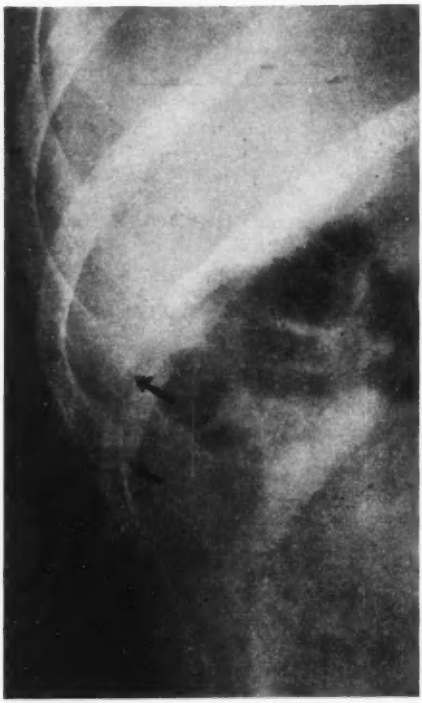

FIG. 5 (*Case* 5).—Nodular enlargements at the costochondral junctions of the lower ribs.

[1]Sussman and Copleman (1942) described a peculiar appearance near the costo-chondral junctions of the lower ribs on both sides in Cushing's syndrome. The ribs at these points are expanded to about twice their normal size for a distance of about one inch. The appearance suggested callus formation and the histological appearance in one case was indistinguishable from callus. These rib nodes were noted in 6 out of 7 cases and their X-ray illustration is identical with that in fig. 5.

was naturally concerned about his altered appearance and he did not mingle with other students. He was finding it increasingly difficult to cope with his studies.

In August 1949 his mental state deteriorated and he failed to sit his examinations. He became markedly depressed and retarded. His appearance showed evidence of personal neglect. Arrangements were made for X-ray therapy and in September 1949, he received 3,000 r in nineteen days. He improved to a fair extent and has recently resumed his studies. His appearance is unchanged but he says he feels better and is not so depressed. Blood count: R.B.C. 5,100,000; Hb 100 per cent. Blood pressure 150/95. His headaches and the distressing sensations of heat and fullness in the face and head have subsided considerably. By the summer of 1950 he had made considerable improvement. He was thinner, less plethoric and more cheerful and alert.

Case 6.—J. W., male, aged 24 years. This patient was a soldier serving in the Middle East who was referred to a military hospital there in 1944. His health had been excellent until a few months previously. His weight on entering the Army in 1940 was 149 lb. During 1943 and 1944 he had put on about 15 lb. and his present weight was 165 lb. Although keen on athletics he had been forced to abandon any physical exertion. He felt extremely tired at the end of the day and for some months had been accustomed to retiring early to his quarters. He also stated that he had changed considerably in appearance. His face had fattened and a photograph he had sent home had caused much comment. In his unit he was often the subject of banter and ribald remark. Apart from these symptoms he remained on duty until early in 1944. He then began to suffer from vague pains in the back and lower limbs and a great increase in his feeling of constant fatigue. He had suffered bouts of severe headache, which were intense. On some days his whole head felt as if it were throbbing and bursting. At such times his face, head and neck were very flushed and the overlying skin felt hot and burning. For three or four months prior to admission to hospital, broad purple streaks had appeared over the lower abdomen. He had shown them to several of his colleagues and eventually to his unit medical officer. They first appeared below the umbilicus and were pink in colour. Soon, they enlarged, deepened in colour and alarmed him. They quickly spread to involve the flanks, groins, buttocks and inner aspect of both thighs. His abdominal wall was tender, and he disliked rubbing it with a towel.

At the time of his admission to hospital he complained of sleeplessness and of being very thirsty. He had spent two previous summers in the Middle East but had not previously experienced this. He noticed no tendency to polyuria. At times he felt short of breath and suffered palpitations with a sense of weakness and suffocation. He sighed repeatedly—taking long deep breaths. He was very worried about himself and although he said he was depressed he remained co-operative and interested while he was in hospital. There did not seem to be any significant depression or retardation. He remained alert, and responded well to reassurance and explanation.

The obesity was confined to the head and trunk. His limbs were quite spare. His face was round and "moon-shaped," and of a dusky red colour (fig. 6). It attracted immediate attention when seen for the first time. His eyes were watery and the conjunctivæ slightly congested. The skin of his neck and shoulders and over the sternum was similarly cyanosed, though to a lesser degree. Livid, purple striæ were present over the lower abdomen and about the buttocks and upper part of the thighs. They were also in evidence about the axillæ and inner aspects of the upper arms. He was slightly kyphotic and there was considerable fatty tissue about the neck and above the clavicles. External genitalia were normal and there was a normal hair distribution. There was no abnormality of the cranial nerves. Optic discs and fundi were normal and vision 6/6 in each eye. Visual fields were normal. In the limbs there was normal power, reflex activity and sensation.

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FIG. 6 (*Case* 6).—General appearance.

Pulse was 85 at rest; blood pressure 150/90. There was no clinical or radiological evidence of cardiac enlargement. No mass or area of tenderness in the abdomen; during examination he complained several times of a curious hyperæthesia about the umbilicus. Urine contained a trace of sugar on most occasions and a fasting blood sugar was estimated at 125 mgm. per 100 c.c. Glucose tolerance curve indicated a moderate degree of diabetes.

Blood count: R.B.C. 5,500,000; Hb 100 per cent, colour-index 1·0, W.B.C. 6,200, normal differential count. Intravenous pyelography was normal. X-ray of skull disclosed no abnormality. X-ray of vertebræ showed no evidence of osteoporosis. Urinary 17-ketosteroids were not estimated.

He remained under observation for about six weeks and was then invalided home. Follow-up has not been possible.

Case 7.—A. W., female, aged 28. She was a "delicate child" and on leaving school at the age of 14 years she remained at home until the age of 18. She had passed the entrance examination of a secondary school but her parents were unable to allow her to proceed with her schooling. She started to menstruate at the age of 13. Periods were regular and lasted eight days. When she was 25 years of age her periods became scanty, lasting only two days. She had been stout for some years but in 1946 weighed 13 st. She became difficult at home. She complained of headaches, giddiness, insomnia, and occasionally of diplopia. She had fits of crying and anger. She served in the Land Army for a few months but left of her own accord. She became a heavy cigarette smoker and her habits were odd. She was very conscious of her gross appearance and was rude and irrational at times. Hair began to appear on her chin and upper lip. She avoided going out and for a year or more rarely visited anyone.

At home she was intolerant, destructive, and given to violent language. She

threatened suicide on many occasions and was once in hospital because she had swallowed some coins. She had bouts of severe depression and agitation but there were no signs of hallucination or delusion. Her memory and orientation were normal. She was finally admitted to a mental hospital in June 1948. By then menstruation was very scanty. She was obese, red-faced, and hirsute. She shaved her face and chin. She had little appetite and constantly asked for sedatives. Headaches, insomnia and depression were her chief complaints. She complained of diplopia on looking in all directions.

There were no changes in power, reflexes or sensation. Optic discs were normal, X-ray of skull was normal, and the blood Wassermann negative. The urine contained a trace of albumen; no sugar. Blood pressure was 140/65. Urinary excretion of 17-ketosteroids was 42·5 mgm. per twenty-four hours. The pubic hair was of masculine distribution.

In September 1948, she was given a course of deep X-ray therapy to the pituitary gland. It was completed in twenty days and she received a total dosage of 4,000 r. By the end of September there was a notable improvement in her physical and mental condition. She had been considered a suicidal risk and was now allowed ground parole. She had less headache, had lost weight, felt better, and was more manageable. She was discharged from hospital in November 1948. During this period of observation no purple striæ were observed about her trunk but she herself thinks that from time to time there were pinkish streaks about her abdomen.

On return home she remained improved for a few months but her condition then relapsed. She was admitted to hospital for further investigation in May 1949. She was then miserable, agitated and complaining much of headaches, insomnia and loss of appetite. As a result of her treatment she said she had lost about 2 st. in weight. Actually, she weighed 9 st. 10 lb. She had a moustache and a small beard. Her limbs and face were hairy. The clitoris was normal and there was no lesion of the uterus or ovaries. The labia minora were hypertrophied. There were no striæ and she was not cyanosed or flushed. R.B.C. 5,020,000, Hb 98 per cent, B.P. 130/70; urine normal. Glucose tolerance was reduced.

0	30	60	90	120	150	min.
96	160	165	163	183	156	mg. per cent blood sugar.

There was no radiological evidence of osteoporosis and the ribs were normal. The cerebrospinal fluid pressure was 120 mm. in the lumber pond; protein in the cerebrospinal fluid was 45 mgm. per cent. Air encephalography revealed no indication of cortical atrophy. Visual acuity was 6/6 in each eye and fields and fundi were normal. Urinary 17-ketosteroids was 11·9 mgm. per twenty-four hours.

She was unstable and difficult to manage. She continually demanded sedatives and complained bitterly of headaches and "awful nights." The nursing staff considered her defective but her intelligence was normal though her memory was very poor. Wechsler differential tests did not suggest intellectual deterioration. The left adrenal gland was exposed (Mr. R. A. Mogg) in view of a suspicious X-ray shadow but no tumour was found. The gland was very vascular, slightly enlarged, and soft.

Discussion

In the 7 cases here reported the development of the physical symptoms and signs of the disease was accompanied by nervous or mental symptoms in 4. In a fifth patient (Case 1), following deep X-ray therapy to the pituitary gland, optic atrophy and dementia ensued. Before assessing the significance of these findings we might consider the experience of other observers. In Table I are briefly recorded examples of published

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TABLE I.—RECORDED NERVOUS AND MENTAL SYMPTOMS IN CUSHING'S SYNDROME

Reference	*Mental symptoms*	*No. of patients*	*Sex*
Anderson	"Restless and mentally disturbed"	1	F
Bland and Goldstein	Psychotic depression	1	F
Blake-Pritchard	"Violet outbursts of temper"	1	F
Cluxton *et al.*	Psychotic: mental hospital	1	F
Crooke	Psychotic depression	1	F
Cushing	Case 2. Anxieties—depression Case 14. Became alert after treatment	2	F
Ellis	Psychotic	1	F
Friedman	Speech hesitant: impaired memory	1	M
Fuller	Depressed, suicidal, mental hospital	1	M
Graef *et al.*	Slow, slovenly, immodest	1	F
Heinbecker	Drowsiness 1 Depression and apathy 1	2	F
Hoyle	Retardation, depression	1	F
Dorfman	Depression	1	M
Klein	Depression	1	F
Lintz	1. Acute confusion 2. Hysteria 3. Psychotic	3	F
Luft	Anxieties, psychotic depression: suicide in 1	9	F 7 M 2
Maclay *et al.*	Depression, suicidal, delusions	1	F
Moehlig	Emotional—psychotic	1	F
Medvei	"Melancholic depression"	7	F 5 M 2
Mooser	Insomnia, dreams, hallucinations	1	M
Northfield	Depression	1	F
Page *et al.*	Slow, drowsy: rambling speech	1	F
Pattison and Swan	One died in mental hospital One died of meningitis	2	F
Thompson and Eisenhardt	3 suicidal deaths. Psychosis not uncommon	3	Not mentioned
Schlesinger and Horwitz	Parkinsonism Psychotic depression: sudden onset	1	F
Williams	Paranoid psychosis	1	F
Wright	"Insomnia, nervousness" 1 Unconscious episodes 3	3	F

cases of Cushing's syndrome in which considerable nervous or mental abnormality is mentioned.

Cushing (1932, 1934) made only passing reference to the intellectual or emotional state of a few of his patients. Some, at least, of his photographs suggest that the patient was depressed or retarded. Case 2, he wrote, had fits of irritability, periods of depression and she was unable to concentrate her mind. She was restless and forgetful. Case 14, after deep X-ray therapy, showed prompt improvement in her general condition and "became alert, interested in her surroundings and soon was engaged in helping the nurses in their ward work."

In one of the earliest cases reported in this country (Turney, 1913), the patient remained "mentally unchanged." A tumour of the left adrenal gland was found at autopsy and the pituitary gland was outwardly normal. Anderson's patient (1915) "became restless and mentally disturbed" and she suffered from insomnia and headaches. Basophilism of the anterior pituitary gland was found at autopsy. Parkes Weber's (1926) case remained mentally normal; she experienced distressing sensations of suffocation.

In the majority of case reports since 1932 the mental state of the patient is not mentioned. In 1938 Maclay *et al.* recorded that out of 49 cases in the literature, including tumours of the adrenal cortex and the thymus, the mental state was only mentioned in 20. However, they concluded from their studies that a "mass of interesting psychiatric literature had been disregarded." Their own patient became psychotic and suicidal in the second year of her illness. Deep X-ray therapy and radon seed implantation of the pituitary gland failed to effect improvement.

The references in Table I are not exhaustive but they are sufficient to indicate that at least 50 reported examples of Cushing's syndrome have suffered considerable nervous or mental distress. Not included in this list are other cases in which minor symptoms such as irritability, nervousness, insomnia and forgetfulness were the only nervous symptoms mentioned. Neither has shyness, feelings of self-consciousness, avoidance of social contacts been included—such as occur in females suffering from adrenocortical virilism (Holmes, 1925; Murray and Simpson, 1927; Brown, 1930; Lescher and Robb-Smith, 1935; Allen *et al.*, 1939; Broster, 1940).

Bauer and Wassing (1913), Rutishauser (1933), Josephson and Bergstrand (1934), Jamin (1934), Schilling (1936) and others make passing reference to nervous features arising in the course of the disease. Jonas (1935) in his long review states that mental disturbance occurred in 20·5 per cent. In some the disturbance is mild and readily overlooked, but in others the psychotic manifestations are obvious. He mentioned mental dullness, forgetfulness, delusions, depression and cyclic psychotic states. Lintz (1941) wrote that in his experience some mental disturbance is present in the majority of cases of Cushing's syndrome. Zondek (1943) mentions depression. Luft's monograph (1946) contains accounts of 11 cases of the syndrome in 9 of which there was considerable mental disturbance. Depression, anxiety, agitation and general emotional instability were common. One patient was admitted to a mental hospital and subsequently committed suicide. Simpson (1948) says that neurosis or mental depression is sometimes met with and that the association is probably not coincidental. Medvei (1949) quotes his experience of 7

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cases of the syndrome in which signs of melancholic depression of varying degree were present in all. 5 were referred for psychiatric opinion.

Of the 50 cases recorded in Table I at least 18 had psychotic disturbances. Depression is the commonest mental symptom, while general anxiety, agitation, emotional instability, and restlessness are also frequently met with. Some patients become suicidal. Thompson and Eisenhardt (1940), reviewing the published cases of the disease, found that there were three suicidal deaths in 58 cases who were ultimately shown to have had pituitary basophil adenomata. They have since heard of other suicides. The suicidal tendencies must be considered as real dangers.

It has been pointed out that treatment by deep X-ray or radon seed implantation of the pituitary gland has on the whole been disappointing. But in some cases there has been striking improvement and where mental disturbances were present they too have responded. Reference has already been made to Cushing's observation on the improved mental state of one of his early patients after irradiation of the pituitary gland. Hoyle's (1933) patient also improved mentally as did Bland and Goldstein's (1937). The latter recorded that "the patient's psychical state improved considerably concurrently with improvement in the dermatological condition." Initially "the appearance of the face was causing her mental depression bordering on a psychosis." Lintz (1941) recorded that of his 3 patients with mental disturbance 2 were treated by deep X-ray to the pituitary. The first was cured rapidly of a confusional episode. She was violent, suicidal, incontinent and disorientated. She recovered in a few months and five years later was in good health. The second patient improved considerably concurrently with return of menstruation and improvement in her general physical condition. Luft (1946) subjected 7 of his patients to deep X-ray treatment and 4 responded satisfactory with relief of mental depression and general nervousness. He regarded this as valuable in view of the danger of psychoses in these patients. Northfield (1939) has observed the relief of psychotic depression following the implantation of two radon seeds (3·7 m.c.) into the pituitary gland.

Ellis (1949) estimated that in 33 out of 60 cases treated by pituitary irradiation there was no improvement. The mental distress may continue. The patient described by Maclay *et al.* (1938) was still extremely depressed and psychotic after completing a course of deep X-ray therapy. The effect of radon seed implantation was no better and the patient subsequently died. The experience of Dorfman *et al.* (1940) in their case was also disappointing and Luft (1946) had two failures. Schlesinger and Horwitz' (1940) patient died, psychotic, following the removal of the left adrenal gland—which contained a benign cortical adenoma.

There is good evidence, therefore, for the inclusion of mental symptoms in a description of the clinical features of Cushing's syndrome. They may occur early or late in the course of the illness and sometimes dominate the clinical picture. As a consequence, the management and treatment of these patients is often difficult.

The relationships between endocrine and mental disorders are necessarily complex. It has not been demonstrated that any purely psychiatric illness can be caused by endocrine disorder and cured by endocrine treatment. Abnormal mental states may be associated with affections such as thyrotoxicosis, acromegaly and hypoparathyroidism, but they are uncommon. In myxœdema, however, such complications are frequently encountered. In calvarial hyperostosis (Morgagni-Stewart-Morel) psychoses are sufficiently common to be included in the clinical syndrome. The adrenogenital syndrome is another such example. No doubt, at least in part, the disfigurement produced in the adrenogenital syndrome accounts for the nature of the mental reaction—with its shyness, ideas of reference and aversion to the male sex.

On the other hand it is well recognized that psychic disturbances can initiate endocrine disorders—such as in amenorrhœa, obesity, or failure of lactation following emotional upset, or hypopituitarism in anorexia nervosa. But the manner in which such sequences come about is not at all clear.

In Cushing's syndrome the patient is certainly handicapped by physical disfigurement. In the female especially this must lead to considerable distress of mind. But there are aspects of the problem which suggest that this is not the whole explanation or even an important one.

Male patients, in whom such a mechanism is less likely to occur, are also liable to mental symptoms. In Table I there are seven such examples and there are probably many more. Then, too, there may be little or no outward disfigurement in the male, as in Case 3 of this series. In that case purple striæ appeared simultaneously with the development of considerable emotional instability. They both gradually subsided over a period of one year. The patient then had an attack of retrobulbar neuritis which left him with a central scotoma. He remained well for a further period of three years, with perhaps some change in his character, before the purple striæ developed anew. His facial appearance altered, but never grossly.

In Case 1 where the appearance was striking there was no emotional disturbance. This is a not uncommon experience as judged from a study of the literature.

Cases 2 and 7 were psychotic at the beginning of the illness—long before the physical changes were such that a diagnosis of Cushing's syndrome was made. They were both admitted to mental hospital in

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the first few months of the illness. Case 7 rapidly improved with deep X-ray therapy to the pituitary gland and was discharged from hospital after five months. There are a number of similar cases already recorded. The rapid and simultaneous improvement in the physical and mental condition of some patients as a result of treatment is suggestive evidence of their both being a manifestation of the underlying disease process.

For these reasons, then, it is considered that in Cushing's syndrome mental disturbance may be a feature of the illness itself.

Neurological and mental disorder following treatment.—Another complication which must be considered is that of optic atrophy and/or dementia following irradiation of the pituitary gland or radon seed implantation. Case 1 of this series was mentally normal before treatment. He made rapid and dramatic improvement in the six months following pituitary irradiation. He received 6,000 r in thirty-two days. His physical appearance returned to normal and his blood pressure dropped from 220/140 to 125/80; purple striæ disappeared. He became quite fit again and returned to normal employment. He remained well for two years but then gradual visual failure and deterioration of his faculties set in. He was able to work for another year and a half but four years after treatment he was blind, incontinent and bedridden. Encephalographic studies showed progressive hydrocephalus and cortical atrophy.

Northfield (1939) has also observed mental deterioration, incontinence and non-obstructive hydrocephalus after treatment for Cushing's syndrome. His patient, a woman aged 30, was previously intelligent and alert. Two courses (2,600 r and 5,061 r) of deep X-ray treatment to the pituitary gland led to slight improvement only. One radon needle (3·7 m.c.) was then inserted into the gland but there was subsequent deterioration, incontinence, visual field defects and ventricular dilation. The patient died and although there was no histological evidence of radionecrosis in the brain the atrophic changes that were present suggested that irradiation had been cumulatively harmful.

Armstrong (1949) has also observed visual failure develop in Cushing's syndrome after pituitary irradiation. His patient received 2,440 r in fifteen days and she lost weight and the characteristic striæ practically disappeared. But six months later she complained of failing vision in the right eye. She subsequently developed bitemporal field defects. The sella turcica remained normal and air encephalography revealed no abnormality; the cisterna chiasmatis was not obliterated. A year after the onset of visual loss her vision was 6/36 R. and 6/18 L. and there was considerable constriction of both visual fields. There was never any evidence of chiasmal pressure.

Ellis (1949) has heard of one case of unilateral blindness developing

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one year following a dose of 5,500 r in three weeks and another case following a dose of 2,440 r in three weeks.

Greene (1951) has had the following experience with one of his patients, a male, aged 42, suffering from acromegaly. The pituitary fossa was enlarged on X-ray but visual acuity, optic discs and visual fields were normal. The excretion of 17-ketosteroids in the urine was 23·3 mg. in the twenty-four hours. The patient was treated by deep X-ray to the pituitary region—4,000 r. The results of treatment were very satisfactory and the patient returned to work. Seven months later, however, his vision began to deteriorate quite rapidly. He was soon blind in the right eye and in the temporal half of the visual field of the left eye. The right disc was pale; there was no œdema and the retina was normal. There was temporal pallor of the left disc; visual acuity 6/12. Chiasmal exploration was performed by Mr. L. C. Oliver. No tumour was found. The relations of both optic nerves and chiasm were normal though there was some indentation of the inferior aspect of the chiasm towards the left as if a tumour had previously been present. The optic nerves and especially the inferior surface of the frontal lobes were slightly reddened. There was no arachnoiditis. The dural roof of the sella was retracted and the contents apparently shrunken. Soon afterwards there was complete bilateral optic atrophy. The patient remains well otherwise.

It will be recalled that in Case 3 of the present series acute unilateral retrobulbar neuritis developed early in the disease. This patient has a permanent central scotoma and has had no treatment.

The ætiology of such complications in Cushing's syndrome is not known but the clinical evidence, such as it stands, certainly suggests that irradiation therapy is a factor in the majority. Pathological studies are necessary.

The clinical and pathological features of necrosis of the brain following radiation therapy have been reported by Pennybacker and Russell (1948). The clinical effects may appear suddenly and progress to a point; or they may come on gradually and lead to death. In each of the 5 cases they reported there was a long latent period between the radiation treatment and the onset of clinical signs of necrosis. The shortest interval was nine months and the longest five years. The lesion was an extensive subcortical necrosis, maximal in the field which received the most radiation. They considered that the necrotic areas developed as a result of reactions in the cerebral blood vessels, in which there was much collagenous thickening, fibrinoid necrosis and thrombosis. In view of these untoward effects they suggest that irradiation of the brain should be reserved for inoperable tumours and for cases in which no further surgical procedures are contemplated.

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Neurohypophyseal mechanisms.—The nervous system does not exert direct control over the secretory activity of most endocrine glands. Only the adrenal medulla and the neurohypophysis possess a rich nerve supply and are directly influenced in their activity through this supply. The more slowly acting endocrine glands are apparently regulated through humoral channels (Harris, 1948). Gellhorn (1942) believes the neurohypophysis is unique in that denervation leads to atrophy of the glands and cessation of secretory activity.

Gross cerebral atrophy is not a feature of Cushing's syndrome. The only cerebral changes mentioned by Heinbecker (1944, 1946) consisted of atrophy of certain hypothalamic nuclei. The hypothalamus was available for study in five of his six cases. In these five there was well marked hyalinization of the basophil cells. In four there were definite changes in the hypothalamic nuclei, particularly the paraventricular. In none of the four was there an adrenal tumour. In the fifth case, in which there was no hypothalamic lesion, there was a malignant adrenal tumour. Heinbecker also found there was a mild degree of internal hydrocephalus in three of the four cases, with which was associated an atrophy of the ependymal lining cells of the third ventricle opposite the paraventricular nuclei. He mentioned also the case of a woman with the characteristic features of Cushing's syndrome, who also had a meningioma of the cervical cord (C2). The C.S.F. pressure on lumbar puncture was 240 mm. Following the removal of the meningioma, the patient's appearance returned to normal within a year. Obesity, hirsutism, plethora, and acne subsided and menstruation became normal again. Heinbecker postulates that internal hydrocephalus produced hypothalamic dysfunction with resultant loss of basophil cells and the production of Cushing's syndrome. If the neural hypophysis of a dog is separated from the supraoptic and paraventricular nuclei there occurs loss of basophil cells in the glandular hypophysis. The eosinophil cells become dominant and there is consequent hyperactivity of the eosinophil-adrenal cortical hormone.

It is not impossible, therefore, that a disturbance of the hypothalamus, with consequent pituitary dysfunction, may account for the concurrent association of mental and physical disorders in Cushing's syndrome. But the role of the hypothalamus in governing or mediating emotional experience remains largely conjectural.

Summary

The clinical features of 7 cases of Cushing's syndrome are described. In 5 there were significant mental and/or neurological disturbances. In Case 1 pituitary irradiation produced apparent clinical cure of the condition but two years later progressive optic atrophy and cerebral atrophy

set in. Four years after treatment the patient was blind, bedridden and incontinent. Two patients (Cases 2 and 7) were psychotic in the early stages of the disease. Case 3 suffered from much emotional instability and was a patient in a neuropsychiatric centre for several months and subsequently developed the physical appearances of Cushing's syndrome. He also had an attack of unilateral retrobular neuritis which left him with a permanent central scotoma. Case 5 suffered from considerable depression and alteration of personality in the first year of his illness.

Attention is drawn to the frequency of mental disorders in Cushing's syndrome as illustrated by a study of published case-histories. 50 cases are quoted.

The complication of injury to the visual tracts and cerebral tissues as a probable result of X-ray therapy is considered in the light of existing experience.

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HYALINE BODIES IN THE OPTIC DISCS: REPORT OF TEN CASES EXEMPLIFYING IMPORTANCE IN NEUROLOGICAL DIAGNOSIS[1]

BY

JOHN W. CHAMBERS and FRANK B. WALSH

HYALINE bodies in the optic discs may account for errors in diagnosis. The appearance of the discs may suggest papillœdema associated with increased intracranial pressure, or optic neuritis; field defects present in some cases may suggest intracranial involvement of the optic pathways. The principal purpose of this paper is to present 10 case reports which illustrate the clinical significance of hyaline bodies in the discs as regards differential diagnosis. In 6 of our 10 cases papillœdema was suspected: in 1 case arachnoiditis was diagnosed; in another serous meningitis was an erroneous diagnosis. As an introduction brief mention is made of occurrence and histology.

Occurrence.—In our experience, hyaline bodies in the optic discs have occurred under several circumstances: (1) as a familial or hereditary anomaly with or without associated symptoms or signs; (2) in tuberous sclerosis; (3) with optic atrophy, when the relationship as regards cause and effect remains unclear; (4) with retinitis pigmentosa; (5) with angioid streaks and pseudoxanthoma elasticum; (6) with high hypermetropia and cystic changes at the macula. Seemingly they occur at any age. Our youngest patient was 9 years of age. When this child was 8 years of age the hyaline bodies were not visible but a year later they protruded from both optic discs. They had not produced symptoms when she was last seen.

Histologic picture.—This has been described by Reese. The masses are composed of hyaline or a closely related substance and frequently there is deposition of calcium which replaces the hyaline. The bodies are situated in front of the lamina cribrosa; while they may extend into the lamina cribrosa they never extend beyond it. Often they are sharply

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demarcated. Usually there is a single principal mass with smaller masses adjacent to it, and occasionally only a single hyaline body is present. From the microscopic picture Reese suggested hyaline bodies are due to excess of immature neuroglia which has undergone degeneration.

Hyaline bodies in the optic discs are dissimilar to colloid bodies which are seen in the retina and originate from Bruch's membrane of the choroid. Also they are unlike corpora amylacea and corpora arenacea which are associated with the pia-arachnoid.

We have been unable to correlate hyaline bodies in the optic discs with specific disease processes. 17 cases from the pathologic material available in the Johns Hopkins Hospital, exclusive of retinitis pigmentosa and tuberous sclerosis, were studied. In no instance were hyaline bodies present when cerebral tumour was a verified diagnosis. However we have recently observed such a case in another hospital. Hyaline bodies were present in the optic discs of 3 glaucomatous cases, in the cases of 2 patients who suffered from syphilis and in the cases of 2 individuals who showed evidences of widespread cerebral degeneration.

Ophthalmoscopic appearance.—Hyaline bodies are waxy or yellow-white; they may be translucent or shiny and rather often are conglomerate and extend from the surface of the disc. They may be buried in greatest part and only a margin of one or more of the bodies may be visible. In some instances the examiner can suspect that hyaline bodies are responsible for elevation and irregularity of the disc in the absence of other signs of papillœdema.

Influence on visual acuity.—In a great majority of cases central vision

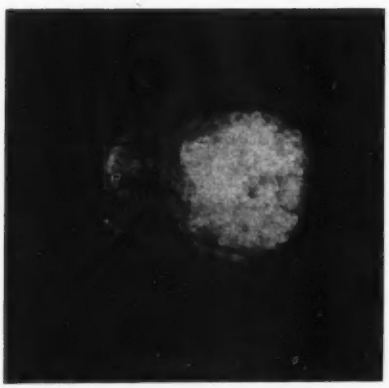

FIG. 1.—Hyaline bodies in the left eye of an individual who required correction of refractive error. Visual acuity with correction of a low grade hyperopic astigmatism was 20/20 for each eye. The blind spot of the left eye was enlarged.

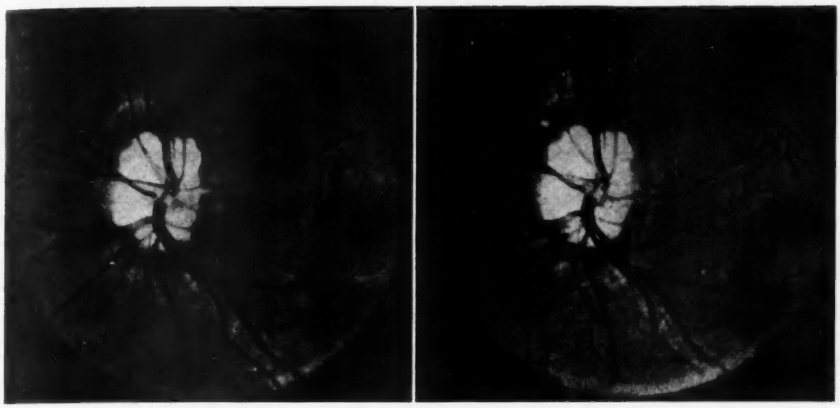

FIG. 2.—Drusen of the optic nerve as a familial anomaly. Stereo-photographs of left eye. (N.S.—114089.)

is uninfluenced by hyaline bodies in the dics. Reese remarked on impairment of vision. We have observed one individual in whom it seemed possible that hyaline bodies were responsible for central scotomas and pronounced loss of central vision with retention of normal peripheral fields (*see* Case 7).

The visual fields.—Both Reese and Rucker described field defects. Often the blind spot is enlarged. Rucker observed narrowing of the lower nasal field as the most characteristic single defect. Also, he observed sector defects, defects extending from the blind spot, and in a single case a ring scotoma. Our cases have exhibited defects similar to those described by Rucker. Central scotomas have not been explained previously on the basis of hyaline bodies in the optic discs.

Progress of the visual field defects.—Although it has been established that hyaline bodies are responsible for defects in the visual fields there is little or no information in the literature as regards progress in the field defects. Through the courtesy of Dr. Tullos O. Coston, Oklahoma City, and Dr. G. Victor Simpson, Washington, we have notes on 3 cases which have been followed for several years. In these cases there has been development of paracentral scotomas in one instance and progressive loss of peripheral field in all 3 cases.

HYALINE BODIES SIMULATING PAPILLŒDEMA

When "choked disc" is an erroneous diagnosis and hyaline bodies are responsible for the ophthalmoscopic picture there is absence of other signs of disease known to be associated with hyaline bodies in the discs (tuberous sclerosis, retinitis pigmentosa). In no instance have we observed hæmorr-

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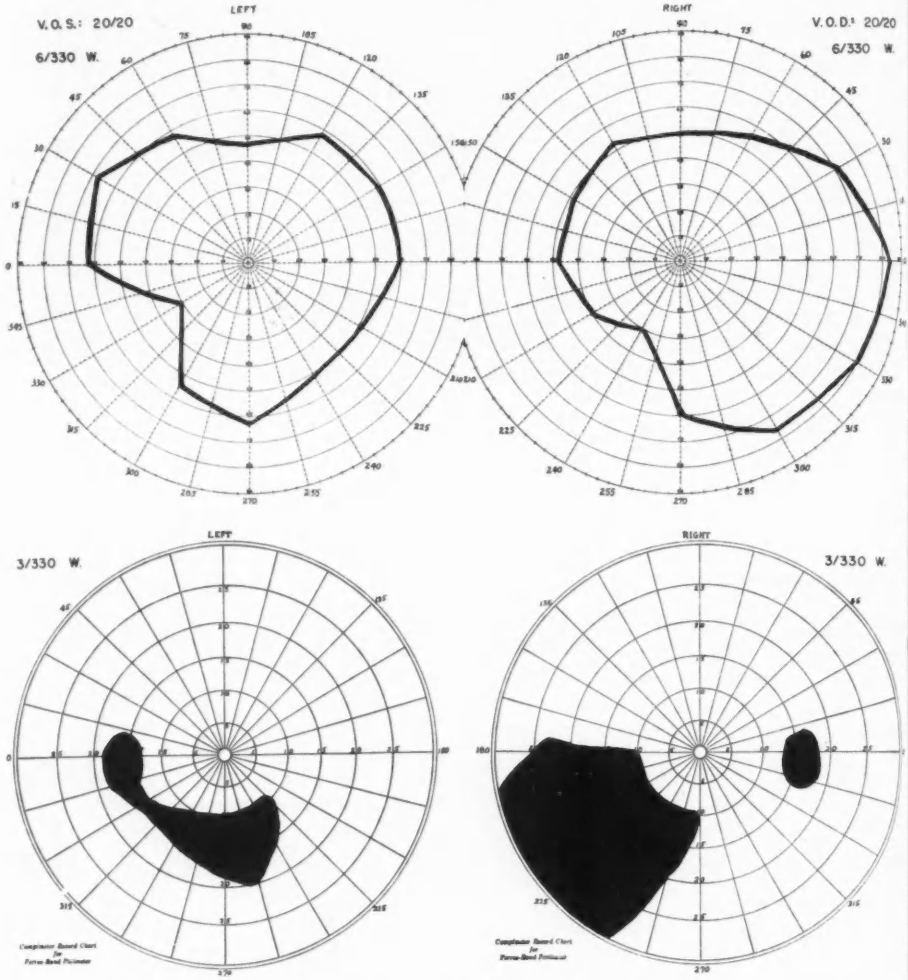

FIG. 3.—F. S., 314653, a woman, aged 33, exhibited hyaline bodies of both optic discs. R.E.V. 20/20; L.E.V. 20/20. All examinations were negative including spinal fluid pressure.

hages or exudates in cases where hyaline bodies were present in the optic discs. The discs have had irregular margins and have definitely protruded forward. In many instances the physiological cup has disappeared. Rather often the veins appear overfilled but this is not usually pronounced. There is a false appearance of choking but œdema of the disc has not characterized the cases we have seen.

In our experience hyaline bodies in the disc often have not been properly evaluated when the patient has had symptoms or signs (headaches, dizziness, convulsions, field defects) suggesting an intracranial lesion associated with increased intracranial pressure.

Case 1.—*42-year-old white male had history of convulsions. Referred as case of cerebral tumour because of "choked discs." Visual field changes were present. Ventriculogram was normal. Hyaline bodies were present in optic discs.*

R. H. L. (357075) was admitted on the neurosurgical service, Johns Hopkins Hospital, July 13, 1948, with a history of convulsions since February 1945. He was referred as a brain tumour with choked discs. The convulsions were nocturnal and occurred almost nightly for one month and then were controlled fairly well with dilantin. The patient had no awareness of the attacks.

On examination the blood pressure was 120/75. Neurological examination was essentially negative except for the findings relating to the eyes.

The eyes were externally normal. Vision: L.E. 20/20; R.E. 20/30. In the right eye the disc was of normal colour except for the upper temporal periphery where there was a golden-yellow scalloped border which was slightly elevated. No physiological cup was present and the vessels appeared full. In the left eye the disc was almost entirely of a golden-yellow colour and the edges were scalloped for the entire circumference. The disc appeared lobulated and just temporal to the exit of the retinal vessels was a small, round vesicle-like object which rested on the disc. The peripheral fundi and maculæ were normal.

There was an inferior nasal cut in the right visual field with enlargement of the blind spot. In the left field there was pronounced constriction (*see* fig. 4).

On July 14, 1948, ventriculography was performed and the ventricular system was normal. The pressure was normal.

The discharge diagnosis was epilepsy of undetermined ætiology.

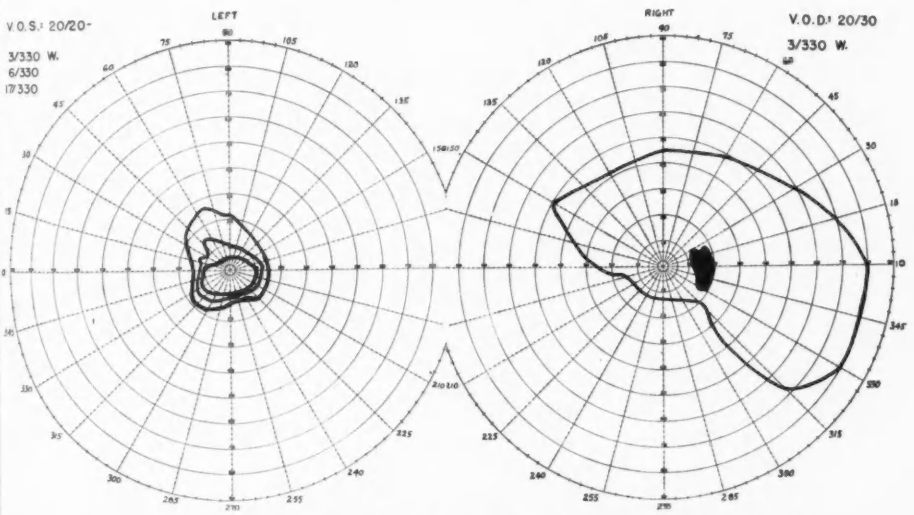

FIG. 4 (*Case* 1).—42 year-old male had history of convulsions. There were hyaline bodies in both optic discs. Air studies were negative.

Case 2.—Headache following trauma erroneously evaluated because of appearance of discs. Referred as cerebral tumour.

F. A. B. (P.P.H. 17468), a 23-year-old white male, was admitted in the summer of 1948 with a complaint of intermittent vertex headache. He had been struck with a missile during a naval engagement about four years before. There was a swelling about the size of a lemon in the mid-parietal region which persisted for several weeks after the trauma. He was seen by a neurologist who thought he had choked discs and made a tentative diagnosis of brain tumour.

General physical examination gave entirely normal findings.

External eye examination was negative, and the visual fields and acuity were entirely normal. Ophthalmoscopic examination revealed the disc margins to be blurred with some elevation. Physiological cups were absent. The blood vessels were normal. Several hyaline bodies could be made out, more pronounced in the left optic disc.*

Lumbar picture showed normal pressure (140 mm. water). Blood and spinal fluid studies were negative. A pneumo-encephalogram demonstrated a normal ventricular system.

Following the air studies the patient ceased complaining of headache.

Case 3.—Headache in patient with hyaline bodies in optic discs accounted for erroneous diagnosis of brain tumour.

P. P., a 19-year-old white male, was seen with a complaint of daily headache, usually left-sided, sometimes suboccipital. He was referred as a brain tumour suspect by an ophthalmologist.

The patient had been in an automobile accident three months before the headaches commenced. At the time of the accident he had been generally bruised but never lost consciousness. With the onset of headaches he became irritable and nervous.

Examination of the eyes was negative except for blurring of both disc margins. Hyaline bodies were present in one eye and probably present but not visible in the other. Visual acuity was 20/20 bilaterally and the visual fields were normal including the blind spots.

Psychiatric examination was performed. It was thought that his complaints were in greatest part present on a psychogenic basis, and that he did not suffer from increased intracranial pressure.

Case 4.—M. M. (468727), a 24-year-old white female, was seen complaining of monocular double vision of three months' duration.

A diagnosis was made of monocular "shadow" diplopia as a result of myopia with astigmatism. Both optic discs had blurred margins and clearly defined hyaline bodies were present bilaterally, more marked on the right. Fields and acuity were normal. It was decided that injection of air was unnecessary.

Case 5.—Unilateral disc abnormality recognized as possibly present on basis of hyaline bodies. Differentiation from papillœdema could not be made with certainty until ventriculography had been performed.

G. S., a white male, 50 years of age, complained of severe headaches of six weeks' duration, also weakness of the right arm and left leg. Two weeks before the onset of severe headaches he noted sensation of shimmering lights followed by mild headaches. Many years before entering hospital he had had transient numbness of the right hand.

General physical and neurological examination gave negative results and only the eye examination revealed interesting findings.

The eyes were externally normal. R.E.V. 20/20; L.E.V. 20/15-4. The optic disc of the right eye had blurred margins and only slight venous pulsation was observed. The disc was hyperæmic. At its nasal side two small hyaline bodies were visible. The retinal veins were full. The macula and the peripheral fundus were normal.

The left optic disc was hyperæmic and on it there was a single hyaline body. Excepting for slight enlargement and the right blind spot the visual fields were normal.

The alleged weaknesses could not be confirmed. It was thought that the patient may have had migraine but it was unsafe to assume that cerebral tumour was absent. An injection of air gave negative results.

Case 6.—*Bilateral disc changes interpreted as choked discs present for four years in man aged* 34. *Hyaline bodies in the discs suspected but not absolutely identified.*

P. W., a white male, 34 years of age, was seen through the courtesy of Dr. R. K. Thompson.

Four years before our examination the patient described transient spells of visual blurring often associated with change of posture. All examinations were negative excepting for spinal fluid pressure which was recorded at 190 mm. and on one occasion 320 mm. A ventriculogram was negative. After this examination the patient ceased having symptoms. However, the ophthalmoscopic picture, namely what was considered to be papillœdema of two dioptres in each eye, remained unchanged. Also the visual acuity, 20/40 for the right eye and 20/20 for the left eye, remained unchanged. Visual field defects (*see* fig. 5) remained unaltered.

One year before our examination the patient was in an automobile accident. He injured his back but was able to return to work as a cab driver in three weeks. He complained of dizzy spells. He was admitted to hospital. The air studies were repeated and again were negative. Spinal fluid pressure was 190 mm.

External examination of the eyes showed them to be normal. R.E.V. 20/40+2; L.E.V. 20/20. Read small print with each eye. Both discs protruded forward two to three dioptres. The margins were blurred. The nasal sides of the discs were flatter than the temporal. Physiological cups were present. The entire discs had a grey colour. The surface of the discs appeared semi-transparent and irregular. In each disc the temporal sides probably contained hyaline bodies but these could

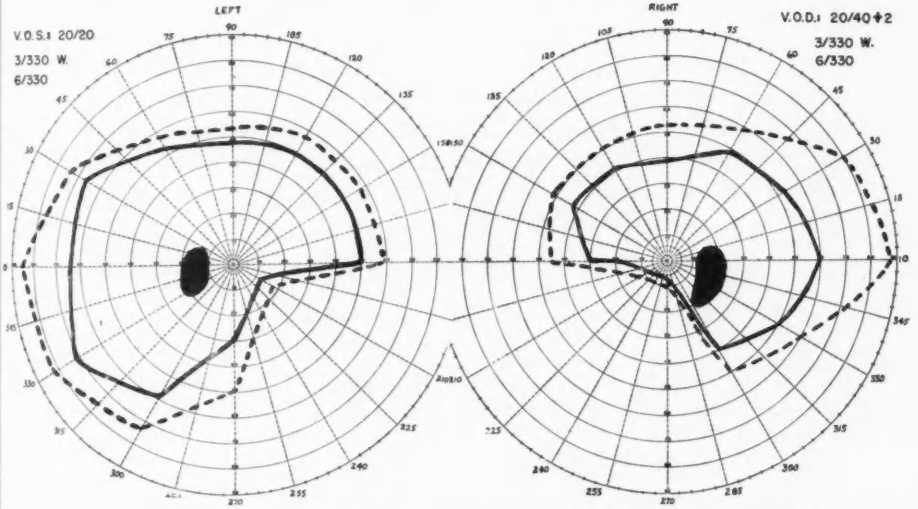

FIG. 5 (*Case* 6).—Field defects present for four years in individual suspected of having had serous meningitis.

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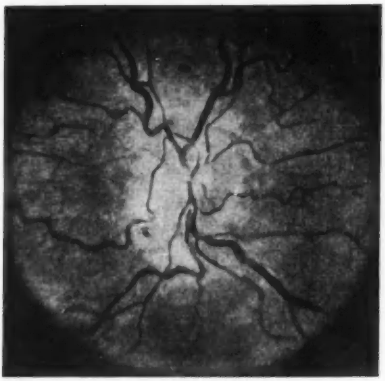

FIG. 6 (*Case* 6).—Fundus picture in individual suspected of having had serous meningitis.

not be identified with certainty. Other than for the discs the fundi appeared normal.

The fields are shown in fig. 5.

Comment.—Hyaline bodies are probably responsible for the picture. The spinal fluid pressures which had been recorded several years before our examination are possibly not reliable in this tense and nervous individual.

CASE CHARACTERIZED BY LOSS OF CENTRAL VISUAL ACUITY

If our conclusion is correct, that hyaline bodies in the disc may be responsible for pronounced loss of central vision when the peripheral fields of vision are full, the case-history which follows is important. We are fully aware that final proof is lacking and passage of time may supply a true diagnosis not now under consideration.

Case 7.—Progressive loss of vision and central scotomas probably due to hyaline bodies.

S. G. (458585), a 65-year-old white male, presented himself on April 26, 1948, for examination. He complained of gradual visual loss in the left eye during several months.

The eyes were normal externally. Vision was 20/30 for the right eye, and counting fingers at two feet for the left. Ophthalmoscopic examination was said to reveal normal fundi excepting for low-grade retinal arteriosclerosis.

The patient was seen during June 1948. The visual acuity of the right was reduced to 20/200 and that of the left eye remained unchanged. There was a five-degree central scotoma in the field of the right eye and a large central scotoma in the left visual field.

He was followed at intervals until October 1948. The visual acuity remained unchanged. At this time it was realized that the right disc was paler than the left

which remained normal in colour. Furthermore it was observed that hyaline bodies were present in the right disc and it seemed probable that the left disc also contained hyaline bodies because the margin of one was barely visible with the binocular ophthalmoscope.

Review of the history emphasized certain important considerations: (1) The loss of vision in the right eye certainly, and according to history in the left also, was gradual. (2) There was no history of excessive use of tobacco and he did not take alcohol. (3) The evidence for vascular lesions consisted only of slight retinal arterial changes. Blood-pressure and general physical examination gave normal findings. (4) X-rays of the skull were negative excepting for slight calcification of internal carotid arteries. (5) A lumbar puncture showed spinal fluid pressure of 90 mm.; Pandy negative; protein 30 mg. per cent; gold curve flat; Wassermann reaction negative. (6) Pneumo-encephalogram was normal.

Cases Characterized by Progressive Loss of Visual Fields

In February 1947, through the courtesy of Dr. Coston, one of us had the opportunity to study a case of hyaline bodies in the optic discs (Case 8).

Case 8.—A man, 41 years of age, had realized for many years that he had some defect in his visual fields. He found that when he walked down stairs he did not have a full field. Dr. Coston found hyaline bodies in both discs. Also he observed the defect in the visual fields of this patient to have increased from September 24, 1946, until January 7, 1947. The visual acuity remained normal for each eye.

Case 9.—An adult male was seen by Dr. Coston in 1940 at which time his visual acuity was 20/25 and 20/13 for the right and left eyes respectively. In 1948 the visual acuity was unchanged but there was slight further concentric constriction of the fields, also a small scotoma for red in each paracentral field.

Since hyaline bodies were visible only in the right disc, it was suggested by Dr. Rucker of the Mayo Clinic who saw the patient with Dr. Coston that he probably had hyaline bodies in the left disc as well and the paracentral defects were so produced.

Through the courtesy of Dr. G. Victor Simpson, Washington, we have observed hyaline bodies in the optic discs accounting for progressive defects in the visual fields. The case is of interest in that it exemplifies confusion between hyaline bodies and opticochiasmatic arachnoiditis.

Case 10.—*A white woman, aged* 29, *discharged from Navy with diagnosis arachnoiditis. Progressive loss of visual fields. Many hyaline bodies in both discs. Negative air injection.*

M. C., a nurse, entered the U.S. Navy in 1945. Her visual acuity with correction was 20/20 for each eye.

Early in 1947 she commenced having headaches and noted difficulty in going down steps at night because of defective vision.

X-rays of the skull, examination of the spinal fluid, E.E.G. and air injection gave normal findings.

The visual fields (*see* figs. 10 and 11) showed progression of the defects. The visual acuity remained normal for each eye.

The patient was discharged from the Navy late in 1947. Early in January 1949 she stated she rarely had headaches.

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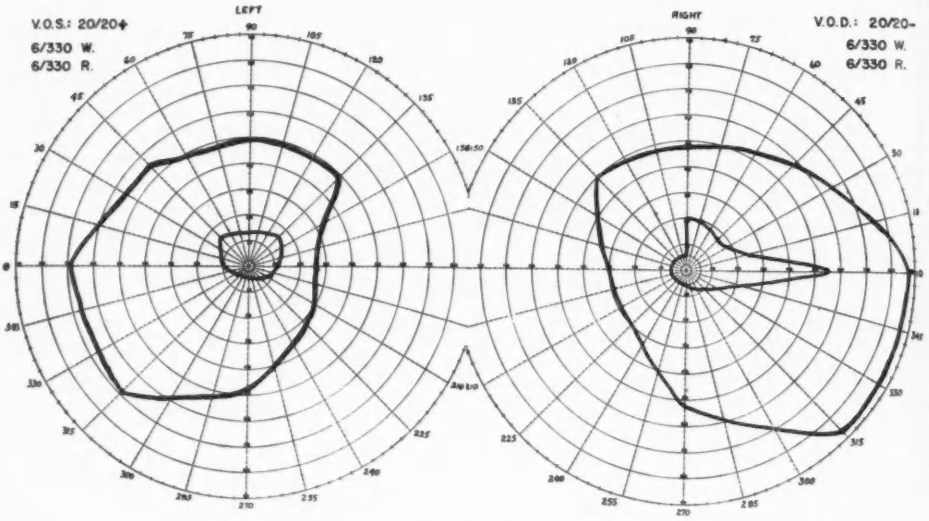

FIG. 7.

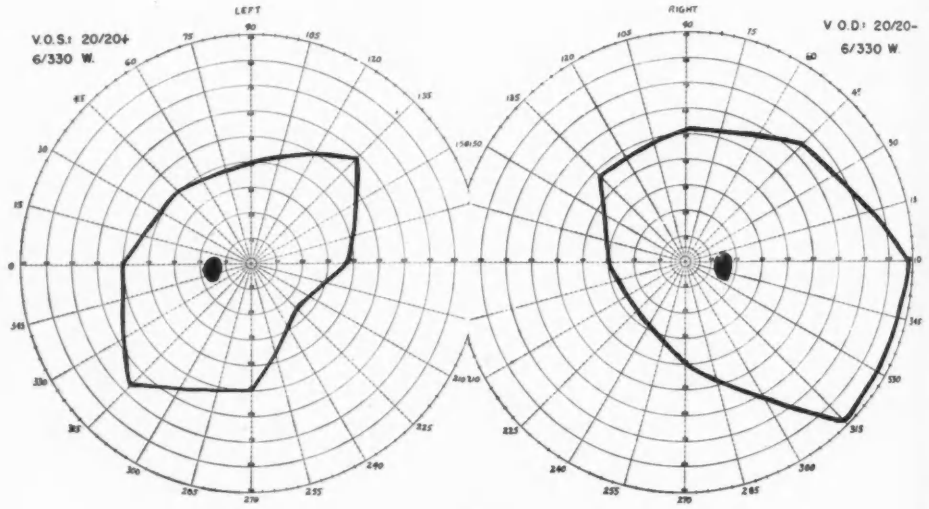

FIG. 8.

FIGS. 7 and 8 (*Case* 8).—Illustrate slight and somewhat questionable increase in field defects associated with hyaline bodies in the optic discs (Coston's case).

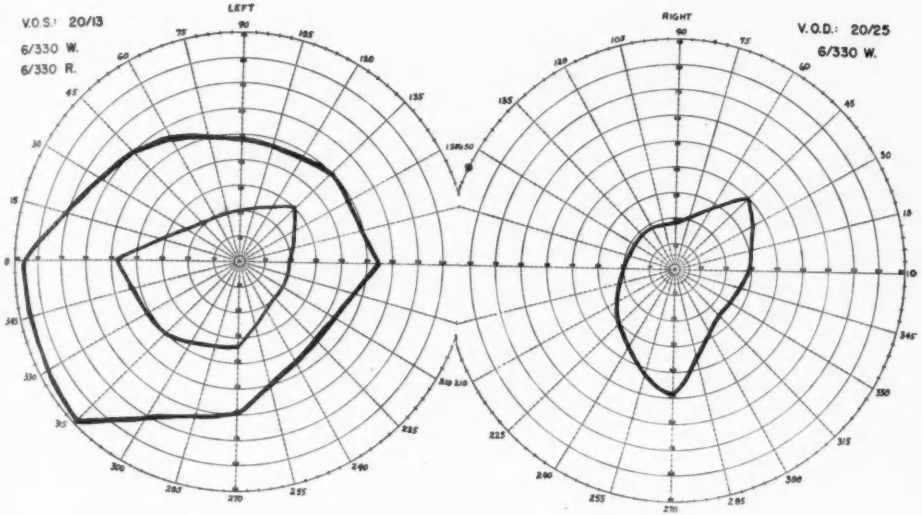

FIG. 9.

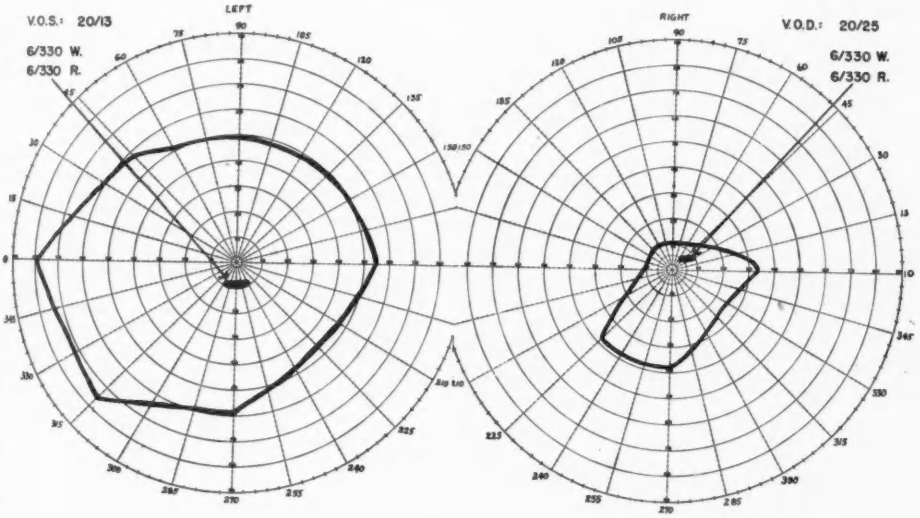

FIG. 10.

FIGS. 9 and 10 (*Case* 9).—Illustrate progress in concentric contraction of field of right eye, also bilateral appearance of paracentral scotomas in both eyes (Coston's case).

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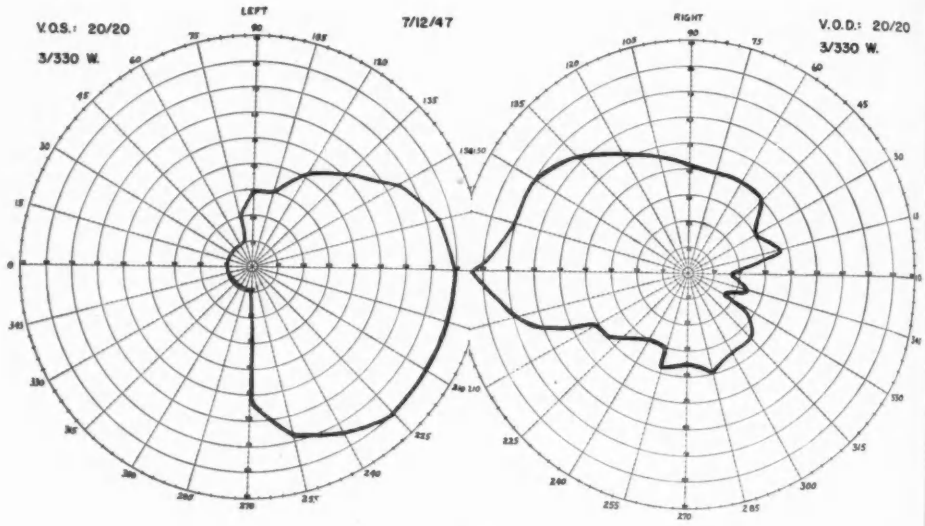

FIG. 11.

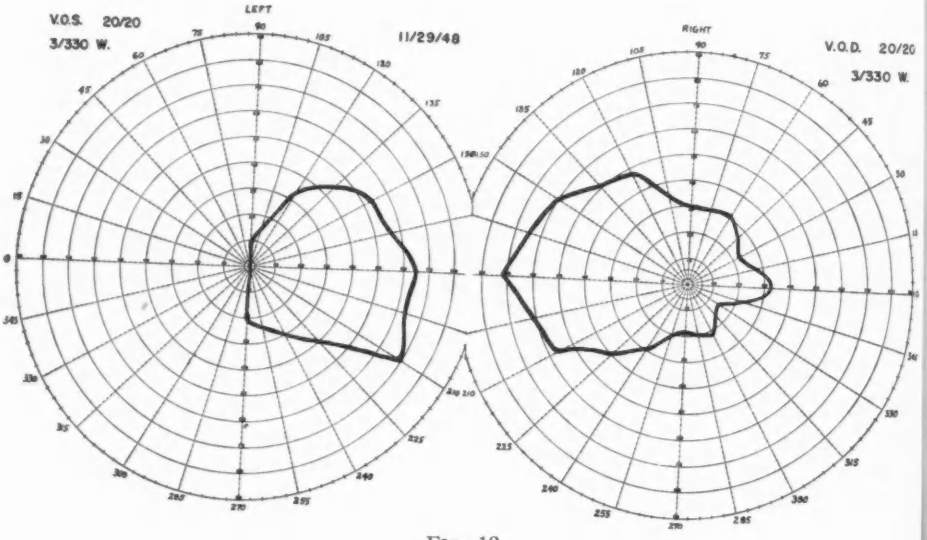

FIG. 12.

FIGS. 11 and 12 (*Case* 10).—Progress in visual field defects associated with hyaline bodies in optic discs. Diagnosis on discharge from U.S. Navy was arachnoiditis (Simpson's case).

Other Interesting Cases of Hyaline Bodies in the Optic Disc

Brief mention is made here of other cases of hyaline bodies in the optic discs which seem of particular interest.

The familial occurrence of hyaline bodies was observed in two sisters. The bodies were discovered during routine refractions. Field defects which were seemingly due to hyaline bodies and might have been confused with homonymous hemianopsia due to post-chiasmal lesion are shown in fig. 3. We have observed hyaline bodies in cases of tuberous sclerosis, retinitis pigmentosa, pseudoxanthoma elasticum and angioid streaks, and high hypermetropia with cystic change in the macula.

Conclusion

(1) Hyaline bodies in the optic discs may suggest papillœdema due to increased intracranial pressure.

(2) In some (but not in all) cases injection of air or other studies to rule out space-occupying lesions may be avoided if the significance of hyaline bodies is realized.

(3) Abnormal visual fields may result from hyaline bodies. Such field defects may progress and may suggest intracranial involvement which is not present.

(4) Some cases labelled as opticochiasmatic arachnoiditis may be explained on the basis of hyaline bodies in the discs.

(5) Our studies suggest that the recognition of hyaline bodies in the optic discs makes intracranial tumour an unlikely diagnosis. In several hundred verified cases of intracranial tumour one example of hyaline bodies in the optic discs was encountered.

Since this paper was sent for publication, actually a few days before the proof arrived, another case worthy of comment came under our observation. Several features are interesting. It points up our inability to give an accurate prognosis as regards ultimate visual acuity in such cases.

Case 11. *White girl, aged 7½ years, was thought to have increased intracranial pressure associated with cerebral tumour. The visual acuity was thought to be decreased. The visual fields were narrowed. Unsuccessful efforts were made to obtain a ventriculogram.*

J. R. had been given visual acuity tests at school. During November 1949 the visual acuity was rated 20/20 for each eye. In February 1950 it was 20/30 for each eye. In February 1951 R.E.V. = 20/80; L.E.V. = 20/70. At that time she was taken to an ophthalmologist who found what he considered to be papillœdema in each eye and narrowing of the visual fields. She was seen in consultation by a neurosurgeon who advised a ventriculogram.

The patient was completely asymptomatic other than as regards defective vision for distant objects.

Roentgenograms of the skull were read as normal. An effort was made to obtain a ventriculogram but was unsuccessful. Then an effort was made to visualize the ventricles by spinal air injection but again the ventricles did not fill. Following

these procedures there was pronounced loss of vision which persisted for three days. Thereafter there was rapid improvement to the preoperative level.

The spinal fluid pressure was said to be increased (no figures given). The protein content of the fluid was said to be normal.

We saw the patient on March 30, 1951, through the courtesy of Dr. Frank R. Ford.

External examination of the eyes showed them to be normal. R.E.V. = 20/80; L.E.V. = 20/40. Retinoscopy under atropine revealed an error of $-1{\cdot}50 = -025 \times 180$ and $-0{\cdot}75 = -1{\cdot}0 \times 180$ for the right and left eyes respectively. With these lenses visual acuity was 20/30 for each eye.

The optic discs protruded between 2–3 dioptres in each eye. Venous pulsation was absent but was produced by very slight pressure. At the upper margin of the right disc a single hyaline body could be seen and several such bodies protruded from the left optic disc. Both discs appeared slightly pale. Other than as stated the fundi were normal.

The visual fields were contracted to approximately 10 degree circles. By doubling the distance between the patient and the tangent screen the fields were widened but not sufficiently to eliminate the suspicion that some of the apparent contraction was functional.

With Dr. Ford we are in agreement that the hyaline bodies in all probability are responsible for the ocular condition. However, we have advised that spinal air injection be performed.

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Notices of Recent Publications

Cerebral Angiography. By P. Almeida Lima, Professor of Neurology. Lisbon Faculty of Medicine. Pp. 221. Illustrations 181. London: Oxford University Press. Geoffrey Cumberlege. Price £2 5s.

Professor Lima collaborated with Professor Egas Moniz from 1926 onwards in the Portuguese Faculty of Medicine. Moniz made the first experiments in cerebral angiography, which was established in Lisbon as a frequently used method of investigation many years before other neurological centres used it more than occasionally. A textbook from this source must be regarded as of importance.

It is therefore interesting to observe that the technique advocated by the author differs radically from that which has found acceptance in almost all other clinics today. Surgical exposures of the common carotid artery, preferably on both sides, is recommended followed by injection of thorotrast into each artery in turn. Elsewhere the percutaneous puncture of the artery has become the routine method. The chief argument put forward by Professor Lima against percutaneous injection of the carotid artery is that puncture of the common carotid artery is essential for diagnostic purposes and that a low percutaneous injection puts the jugular vein at risk. In the many centres where percutaneous angiography is practised the argument for reversion to surgical exposure will probably not be accepted, as little difficulty has been reported in obtaining puncture of the common carotid and no trouble from damage to the jugular vein. The use of thorotrast as a contrast medium will also be regarded as highly controversial, in view of its radioactivity and other reported after-effects. The arguments for and against its use are stated at length in the text.

From the radiological viewpoint the little use made of antero-posterior projections is surprising, though it is stated that antero-posterior projections are made if thought necessary. Among the many illustrations only one normal and three abnormal antero-posterior projections are included, whereas in several of the cases, where the changes in the lateral views are fully described, an antero-posterior view would have given more clear diagnostic information. No mention is made of the value of oblique projections for the exact localization of aneurisms.

An excellent account of the development of the technique of angiography and of the anatomy of the cerebral vessels as thus seen is given and there is much valuable material illustrating vascular displacement by space occupying lesions and vascular abnormalities. The patterns produced by various types of intracranial neoplasms are discussed at some length, but it is felt that, until technical advances permit of some form of cinematograph record of angiograms, the significance of such patterns must remain speculative in many cases. The production of the book is very good, and the diagrams clearly explain the very large number of X-ray negatives reproduced.

The views on technique of a neurosurgeon so experienced in cerebral angiography as Professor Lima are challenging, and his book will interest neurologists, neurosurgeons and radiologists. The percutaneous angiographic technique has probably come to stay, but no contrast medium at present available is entirely satisfactory, and search for something better may well be stimulated by this book.

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Studies on Tumour Formation. By G. W. DE NICHOLSON. 1950. Pp. 637 with 183 figures in text. London: Butterworth and Co. Price £3 3s.

The republication of these twenty essays by the late Professor Nicholson gives us a statement of a biological point of view which is often forgotten.

The intimate, discursive style of the essays is perhaps more suited to the hospital journal, in which they first appeared, than to a scientific treatise but out of what seems, at times, a confusing welter of descriptions of tumours, polemics and epigrams the author's views gradually emerge, to be summed up in the final chapter. They may be briefly stated as follows:

(1) The Cohnheim-Ribbert hypothesis of the origin of tumours in cell-rests, has no foundation in scientific fact, and most observations on the behaviour of displaced tissues contradict it. "Personally I regard every *pre-formationist* theory not only as non-proven, but as reduced to an absurdity and thereby disproven" (p. 163). "There is no difference of principle between a congenital and an acquired tumour, just as every somatic organ is congenital and acquired. For it is congenital in that it is determined at the union of the parental gametes by innate constitution of the resulting organism and acquired in that it is a reaction to excitation." "We have no *a priori* reason whatsoever to suppose that these ('embryonic tissue malformation,' 'cell rests' and so-called *vitia primæ* formations) behave differently in principle from regenerations or other disturbances of growth 'accidentally' produced in a centenarian. . . . Contrary to accepted belief 'congenital' malformations typically and almost invariably behave precisely like those 'acquired' in later life, by undergoing physiological differentiation at the earliest possible opportunity." They "are not predisposed for tumour formation. At most they are not immune, sharing this disability with physiological somatic tissues" (pp. 328-329).

(2) "Disease (including tumour formation) is the sum of the physiological reactions (of the organism) to unusual and abnormal stimuli" (p. 261). "Extrinsic stimuli and internal reactions together determine tumour formation" (p. 262). At some time, often a long time before the tumour begins its growth, there has been an external stimulus, or series of stimuli, which start it. "With one exception we see nothing in genesis or tumour formation that does not conform in nature and principle with somatic development, and is unnatural, unbiological or unphysiological. The solitary exception is the stimulus, the adventitious factor of realization acting upon living cells from the outside. This alone is pathological, whereas the innate reactions of the organism, whose sum is the malignant tumour, are entirely physiological in the circumstances" (p. 322).

(3) Having been thus started the tumour resembles in its behaviour the tissues of the developing organism. Tumour formation is a resumed or continued ontogency and in it there "is a permanent shifting of physiological balance between rate of growth and physiological action in the direction of the former, with consequent diminution in histological differentiation." (Incidentally this is almost the only place where de-differentiation is mentioned. The word "anaplasia" does not appear in the index).

(4) The organism, that is the "normal" tissues of the body, accepts the tumours and "reacts to them as to flesh of its flesh." "The organism is prepared to do more than acknowledge and maintain its tumours; . . . it will react to them as to its physiological somatic tissues." . . . "Physiological co-ordination and organismal control are defective rather than 'absent.'" "The organism has no respect for the views held by pathology and deals with its tumours as appears good in its own eyes" (p. 288). Sometimes, unfortunately very rarely, a tumour is actually of benefit, temporarily, to the organism, as in a case where secondary growths of a thyroid carcinoma cured the myxœdema which had resulted from the removal of the original tumour.

The author realizes that it is difficult for pathologists to accept a malignant tumour as growing physiologically. This difficulty is due to the tendency to consider phenomena promoting health as natural and those inimical to health as unnatural. To the author this is quite unscientific as biology makes no such distinction. There are other statements with which some pathologists may disagree, among them the following (footnote to p. 299): "It must be a rare event for an established innocent tumour, distinct from nodular hyperplasia, to 'become malignant.' Fibromata, adenomata, etc., said to 'become malignant' are pretty well always malignant from the beginning." Such dogmatic statements, with which the essays abound, serve a useful purpose in disturbing the complacent generalizations which pathologists are apt to accept.

This full discussion of the basic problems of tumour formation, combined as it is with much philosophy and wit, should make the book very welcome to all those interested in the pathology of tumours, and especially of intracranial tumours, in the early classifications of which the Cohnheim-Ribbert hypothesis played so dominant a role. While it is difficult to avoid the view that some intracranial tumours, especially the supra-pituitary epithelial tumours of childhood (called *cranio-pharyngiomata*, with more respect for euphony than for ontogeny) have a developmenal basis, Professor Nicholson's essays should make us look beyond this factor in seeking for their origin.

In his last essay he hopes that he has presented his views without special pleading, and if there has been undue repetition in the various essays, he justifies this by the necessities of polemics, tersely expressed by Lewis Carroll in the line: "What I tell you three times is true."

J. G. G.

Cranioplasty. By D. L. Reeves. Charles C. Thomas, U.S.A. 1950. Pp. 132. Illustrations 71.

The author reviews the history of attempts to close cranial defects with bone and foreign materials and describes the various operative techniques. The indications for cranioplasty are considered and brief reports of personal cases illustrating the method and results of operation in different types of case appended. The monograph is well illustrated and an extensive bibliography is provided.

Psychotic Art. By Francis Reitman, M.D., D.P.M., 1950. Pp. x, 180. London: Routledge & Kegan Paul Ltd. Price 16s.

The term "psychotic art" is an unhappy one, and is really as inappropriate as "tuberculous art" or "diabetic art." What is intended, of course, is a digression upon the creative visual artistic products of the insane. Here again it would be necessary to distinguish between the work of a professional artist who has lost his reason, from that of the psychotic amateur whether it be spontaneous or prompted. Following Clive Bell we can isolate as the one common feature possessed by all works of art, certain combinations of line and colour depicted in such a way as to stir our asthetic emotions. This complex may be termed "significant form" and it is a matter of relative indifference whether this be effected deliberately by an inspired artist, or subconsciously by a lunatic, or automatically by a paint brush fastened to the tail of a donkey. Having made these criticisms, one can turn with interest to this thoughtful and well-written book. "Psychotic art," so-called, usually means schizophrenic art, for demented and depressed patients are rarely capable of a willingness to embark upon artistic undertakings. The author hazards certain generalizations regarding the pictorial achievements of schizophrenic patients. He draws attention to their bolder use of colour, often of violent and unpleasing quality, and at variance with those

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existing in nature. Form and colour may be dissociated. Excessive ornamentation may be noted, especially in deteriorating patients. The question of composite figures, as, for example, the cephalapode, leads on to a discussion of the *modus operandi* of schizophrenic art, and to disorders in the patient's body-scheme (the term "body-image" is disliked). On this matter, the author's psychologist-colleague, Mr. J. P. S. Robertson, has rightly criticized a tendency to include a number of diverse conceptions under the single term "body-scheme." But it must be recalled that the original neurological definitions of the body-scheme were perfectly clear and unequivocal, and that any present-day vagueness of thought is to be laid at the doors of subsequent psychiatric writers who have read more into the scheme than was intended. With these ideas in mind, the author comes to the conclusion that the paintings of the schizophrenic artist are the expression of his inner experience, and that the disjointed limbs and other anatomical distortions which appear in his art betray the fragmentation of his own personality. In schizophrenics, symbols become identical with meaning and are reproduced as such.

The Cerebral Cortex of Man: A Clinical Study of Localization of Function. By W. Penfield and T. Rasmussen. 1950. New York: Macmillan Co. Price 48s. 6d.

The present monograph is an amplification of earlier writings of Penfield and his collaborators on the cerebral cortex, and particularly of his paper with Boldrey published in this journal in 1937, and will be read with critical interest by those who are familiar with Penfield's views on the relationship of the cerebral cortex to the diencephalon, and of both to those states or functions which we commonly subsume under the abstract term "consciousness."

In essence it is the detailed record of punctate electrical stimulation of various regions of the cerebral cortex in no less than 500 sentient human subjects who have come to operation for the surgical treatment of expanding or of atrophic lesions. In this long series, the labour of many years, the cortex may almost be said to have been electrically stimulated from truck to keel, from stem to stern, and the bulk of the monograph consists of the simple protocols of all these procedures, together with the authors' views on cortical function—in particular motor and sensory functions. While these views derive in part from their own observations, they do not do so wholly. Much of their theoretical exposition does not flow from anything they have observed, but is speculative and, in one important matter, the relation of cortex to diencephalon seems to be built round an aphorism of Herbert Spencer's that Jackson frequently cites in his writings. But Jackson, unlike the present authors, did not make this aphorism the foundation of an hypothesis of function, but cited it as a generalization adequate to account for his own clinical observations. Here is a vital difference, which the present authors seem not to have realized. A philosophic aphorism is scientifically valid only when it is a generalization of facts observed. To reverse the process is to put the cart before the horse.

Thus it is that, in the judgment of the present review, the monograph must be considered first as a record of observations, and separately as an expression of the authors' views on plan of cortical organization.

In their extensive studies the movements seen, and the sensations vouched for by sentient patients, are recorded in respect of many cortical regions, sensorimotor, auditory, visual and those related to articulate speech.

In their quality these observations are not new, they are simply more extensive than any carried out before, and thus the phenomena noted are more numerous. A single general type of stimulation has been employed namely, cycles of stimulation of 60 to 65 cycles per second, of voltages ranging from half a volt to 30

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volts, occasionally 60 or 70 volts. There is no clear indication that they have realized that what ensues from electrical stimulation of the cortex is a function of many variables: form, duration, strength and sequence of stimuli; the prior activity of the regions stimulated and the length and tone of the muscles concerned in movements prior to stimulation.

It is only within the past few years that the importance of all this has been appreciated by experimental physiologists, yet without the full understanding of what it involves, the significance of movements evoked by cortical stimulation, and of the pattern of topographical distribution of movements on the cortical surface as we see them pictured on the familiar maps, cannot easily be determined.

In other words, the movements we see on punctate electrical stimulation of the cortex are no more than raw material, one item of the many data that have to be correlated before any sketch of the plan of the cortical organization of movement can be drawn. Their interpretation in terms of function is a problem of great complexity, as Von Monakow in a penetrating paper pointed out many years ago (*Ergeb. Physiol.*, 1913). It is a problem that has of necessity concerned the clinical neurologist whose daily work forces upon him the realization that symptoms and functions are very different things. The experimentalist has rarely thought of his problem in these terms, nor conceived of the results of his stimulations and ablations of the cortex as symptoms; as disorders not necessarily directly revealing the functions of the disordered part.

The point is no mere dialectical one, but one that involves the whole question of experimental techniques and their results. The probability, now increasingly realized in the physical sciences that experimental methods may tell us more of their own nature than of the nature of the bodies, or the processes, studied by them, has not widely reached the awareness of neurophysiologists.

Even measurements may tell us more about the properties of measuring instruments than of the properties of the bodies measured. Nowhere in the field of biology has the recognition of all this been more tardy than in that of cortical physiology, and thus it is that we find so many naïve and conflicting interpretations of the results of cortical electrical stimulation. Nevertheless, it is at long last being realized that what happens when the cortex is electrically stimulated is not necessarily a clear reflexion of normal cortical function, but the sum of many variables not all related to normal cortical activity. The recent paper by Liddell and Phillips (*Brain*, 1950, **73**, 125) has clearly shown this, and the problem is one that can no longer be evaded by those who employ the various modes of electrical stimulation.

The authors' studies, dating back many years, naturally show the defects of insight inherent in a failure to understand this problem, as we see in a statement (p. 218) to the effect that "we are faced by an apparent paradox. The evidence from epileptic discharge and from electrical stimulation is that there is represented only elementary movements such as might be expected of an infant, and yet ablation of the precentral gyrus produces paralysis of all the complicated, skilful movements which do not seem to be represented there." There are no grounds in experience or reason for expecting electrical stimulation to reveal all that is represented in the stimulated region, or even that what it does reveal bears an easily recognized relation to normal function.

The authors adopt the conception earlier expounded by Bastian, Horsley and others of a sensorimotor cortex, rather than of a motor cortex and a sensory cortex separately, but in discussing the results of precentral lesions upon sensory function they have overlooked Head's extensive and minute studies of the sensory defects ensuing upon focal lesions of this region. They say (p. 23) that "results of ablation of the precentral gyrus show that little or no sensory deficit is produced, as far as ordinary clinical methods of examination are concerned, despite the fact that 25 per cent of the sensory responses to electrical stimulation were

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precentral in location. It is conceivable, however, that refined quantitative methods might reveal a constant and definite sensory deficit." Yet in *Brain* (1948, **41**, 1) Head had already shown by refined quantitative methods which Holmes and he had devised that specific sensory defects do ensue upon focal precentral destroying lesions, and had defined the different aspects of cortical sensory function affected; showing them, indeed, to have those spatial separations of each aspect that Lashley has postulated as probably a characteristic of cortical representation (*Arch. Neurol. Psychiat.*, 1937, **38**, 371).

In the final chapter on the integration of function in the cerebral cortex we find a grave confusion of thought that vitiates their final conclusion. They quote the aphorism of Herbert Spencer's—so often cited by Jackson, but to different purpose—that "the seat of consciousness is that nervous centre to which mediately or immediately the most heterogeneous impressions are brought." This is the text of their thesis upon the relation of cortex to diencephalon, and of the latter structure to "consciousness." It opens thus, "popular tradition, which seems to be largely shared by scientific men, has taken it for granted that the cortex is a sort of essential organ for the purposes of thinking and consciousness, and that final integration of neural mechanisms take place in it." If scientists do hold such views, we may assume that they do upon scientific evidence of some kind. Surely, it would be absurd to propose that the familiar conclusions as to cortical dominance that we have all read in Sherrington's "Integrative Action of the Nervous System" have a foundation only—or primarily—in popular tradition. Yet this is what by clear implication the authors ask us to accept, in a chapter which is in effect a complete repudiation of the famous eighth and ninth chapters of this work, and is no compliment to their readers.

The argument continues in quasi-syllogistic fashion thus: the diencephalon is the seat to which the most heterogeneous impressions are brought. Therefore the diencephalon is the seat of consciousness and of the final integration of neural function, for "within the diencephalon there are neurone circuits which may be considered the highest level of neuronal representation and re-representation . . . from it there go out effector neuronal impulses that are capable of summoning a memory, of causing the lips to speak, or the arm to move." To this is appended a qualification that makes nonsense of it, namely, "much of the function of this (diencephalic) level is made possible by the special areas of the cerebral cortex. It is therefore inaccurate to say that the cortex belongs to a lower level of activity." Thus, the diencephalon both is and is not the highest level in the neural hierarchy, and in an easy sentence logic and the cerebral cortex are put in their places.

If we recast Spencer's aphorism in terms consonant with what we know of the afferent pathway, it must read "the diencephalon is the centre *through which pass, and in which are relayed,* the most heterogeneous impressions on their way to their final terminus the cerebral cortex." This, surely, is the truth as far as we at present know it.

Yet if not all will find it possible to accept the authors' cortical physiology, we can yet recognize the technical skill and infinite labour they have given to their task. Time will show the value of their observations to the neurosurgeon, and later re-interpretations may reveal their significance in terms of cortical function.

F. M. R. W.

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